Chernobyl and Thyroid Cancer

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The most dramatic effect of exposure to fallout from the Chernobyl accident on physical health has been the increase in thyroid cancer. When this was first reported [1,2], there was scepticism in Europe and the US, as it was not thought plausible that exposure to radio-isotopes of iodine in fallout could lead to such an increase in thyroid cancer with such a short latency. This review will discuss the lessons to be learnt from a re-examination of the reasons for the original scepticism, together with what is currently known about the factors that have influenced the development of excess thyroid cancers in those exposed, the number and type of cancers that have occurred, and the interaction between tumor morphology, molecular pathology, clinical behavior, and latent period.


KEY WORDS: chernobyl; thyroid; cancer

THE ACCIDENT

To set the scene, it is necessary to review briefly the accident on April 26th, 1986, and the immediate aftermath. The nuclear power plant site at Chernobyl in the far north of Ukraine, at that time a part of the USSR, contained four reactors, and more were planned. The reactors were built in pairs, and were of the RBMK type, with graphite cores, lacking the additional outer shell (“secondary containment”) found in modern western reactors. Reactor number 4 was due for a periodic shutdown, and was to be the subject of a test of the ability of the inertia in the moving components of the system to maintain water circulation without the emergency auxiliary pumps. If successful, this would be an additional safety factor. The test, therefore, required that the automatic cut-in of the emergency pumps if a power failure occurred should be disabled. In the event the test failed, to bring more power to the pumps quickly, control rods were withdrawn from the reactor, the combination of inadequate water circulation and rapidly increasing reactor power led to a rapid rise in temperature, a steam explosion which blew the massive lid off the reactor, a runaway reaction which could not be controlled, and a fire in the graphite core. This led to the release of huge amounts of radioactive isotopes.

The fuel in a nuclear reactor decays through a cascade of events, giving rise among other elements to isotopes of iodine which further decay to xenon. The disaster at Chernobyl was not a nuclear explosion but a steam explosion and a fire which led to the release of a high proportion of the volatile elements present in the reactor; the great majority of the non-volatile elements such as uranium are still in the reactor, they formed a molten mass which eventually solidified having sunk through several floors. The radioactive cloud containing the volatile isotopes initially drifted northwest; the first indication to the rest of the world that there had been a major nuclear accident came from nuclear power stations in Finland and Sweden, when the monitors to check their own releases were triggered.

The immediate consequences to the population living around the reactor were the result of fear of the unknown and distrust of government reassurances, together with the direct effect of forced evacuation for well over a hundred thousand people. The immediate consequences for those working in or immediately around the reactor while the accident was taking place and shortly afterwards included acute radiation sickness from whole body exposure in about 150 people, with 28 deaths in the short term, and about 20 more probably radiation related since

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Received 23 August 2006; Accepted 28 August 2006
DOI 10.1002/jso.20699
Published online in Wiley InterScience (www.interscience.wiley.com).

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that time. The first serious physical health consequence noted in the millions exposed to fallout in the three most exposed countries—Belarus, Ukraine, and the Russian Federation—was a sudden increase in the numbers of thyroid carcinomas occurring in children, first noticed in 1990, 4 years after the accident.

**POPULATION EXPOSURE**

Current understanding of the effects of radiation on man is largely based on studies of the population exposed to the effects of the atomic bomb in Japan. The exposure of this population was almost entirely to whole body radiation from gamma rays and neutrons; exposure to more than about 5 Gy led to death. About 80,000 people with known radiation doses are still being followed, and new consequences of radiation exposure recorded. Those working close to the damaged Chernobyl reactor in the immediate aftermath of the accident were exposed to whole body radiation, with effects comparable to those seen after atomic bomb exposure.

In contrast, the general population after Chernobyl was not exposed to significant amounts of whole body radiation, but to beta and gamma radiation from radioactive isotopes in fallout. Many millions of people in Belarus, northern Ukraine, and adjacent parts of the Russian Federation were exposed to significant fallout. Not only does the type of radiation exposure differ, but also does the tissue distribution and dose rate. Atomic bomb exposure led to a relatively uniform tissue dose, and a very high dose rate; after exposure to fallout from Chernobyl, the tissue dose was non-uniform, and depended on the isotopes in the fallout, and the dose rate was relatively low. The largest human exposure was to Iodine 131 so that the thyroid received much larger doses than other tissues—of the order of 500–1,000 times the average non-thyroid tissue dose for iodine isotopes. The thyroid dose for those living close to the reactor was in some cases greater than the dose received by any tissue in the survivors of the atomic bomb. The situation was complex, as the ratios of the different isotopes emitted varied during the week to 10 days of active emissions from the reactor, and varied also with the time between the emission and the fallout. Eight days after the accident, the radiation cloud was still present over Europe; by this time, one half-life of Iodine 131 and over two half-lives of Iodine 132 derived from tellurium 132 would have elapsed. It follows that experience of the consequences of exposure to the atomic bombs may not apply to exposure to fallout after Chernobyl, and also that, partly because of the different types of exposure, and partly because of the much larger number of people exposed, much important information has been and will continue to be gained from the studies of the consequences of the Chernobyl accident.

Iodine-131, together with $^{132\text{I}}$ and $^{133\text{I}}$ formed a high proportion of the radioisotopes released; the very short half-life of $^{133\text{I}}$ meant that it was relevant only to those very close to the reactor. $^{135\text{I}}$, with a half-life of a few hours, although continually replenished from the $^{132\text{Te}}$Tellurium released with a half-life of 3 days was also of less importance than $^{131\text{I}}$ with a half-life of 8 days. The estimates from the amount of $^{131\text{I}}$ released vary, but are of the order of $1.7 \times 10^{18}$ Bq (4.6 $\times 10^{7}$ Ci). Other isotopes released in significant amounts included Cesium 134 and 137. The exposure of the population depended on the position of the cloud, its dispersion, the amount of rainfall, and especially for iodine, the time elapsed since release from the reactor. By far, the greatest exposure took place in the areas immediately around the reactor (a 30 Km zone was evacuated), and in the southern part of Belarus particularly the province (oblast) of Gomel. Much of the rest of Belarus, the northern part of Ukraine and adjacent oblasts of the Russian Federation were also affected, and smaller amounts of fallout occurred in large parts of Europe, for example, some areas in Austria, and the Italian and French Alps. Trace amounts of radioactivity were detected around the northern Hemisphere, including the US, but amounts here were extremely low, far less than from atomic testing in Nevada. Iodine$^{131}$ is rapidly lost from the environment; a very small amount of $^{129\text{I}}$, with an extremely long half-life was released, and measurement of this has been used to estimate $^{131\text{I}}$ fallout. Cesium$^{137}$ with a 30-year half-life also persists in the environment. Some mountainous areas in Wales and northern England which received rainfall when the cloud was passing over still have restrictions on the use of meat from grazing sheep because of the Cs$^{137}$ content, 20 years later. The total amount of $^{131\text{I}}$ released from Chernobyl can be compared with the release from a number of other nuclear events. (Table I)

The fact that a major nuclear power plant accident was likely to be accompanied by a large release of radioactive isotopes of iodine was well known, and measurements of the thyroid uptake of radioactivity were made, but in the crisis that followed the accident, few were made until a week or more later. Thyroid dose calculations have, therefore, depended on reconstruction, either using the direct measurements that were made or estimating radioiodine doses from measurements of Cs or $^{129\text{I}}$ deposition. Little effective distribution of stable iodine prophylaxis to block uptake of radioisotopes of iodine was made at the time, indeed the majority of the population were not told of the dangers until days after the accident, children continued to play outside and continued to drink cow’s milk. Milk of course is the main route through which radioiodines in fallout are ingested, the fallout on the
grass is eaten by cows, and the cow’s mammary epithelium concentrates the iodine. Many in the exposed villages kept their own cow, shortening the time between fallout and ingestion. Because of the irregular nature of the fallout, doses do not depend only on distance from the reactor. In children under 1 year of age in Gomel, 50% of the thyroid doses were greater than 1 Gy, with 34% greater than 2 Gy. The corresponding figures for 16–18 years were 16% and 6.1% [3], (Table II). The considerably greater thyroid doses to children than adults can be attributed to a higher intake because children drink more milk, together with a higher uptake by the gland.

THYROID CANCER

The first evidence of an increase in thyroid cancer came in 1990, when physicians in Minsk, the capital of Belarus, and Kiev, the capital of Ukraine noticed increased numbers of thyroid cancer in children, only 4 years after the accident. In retrospect, there may have been a small increase in less than 4 years. Their reports led to a visit by a small group to Minsk in 1992, arranged by WHO Europe, followed by two letters to Nature, one giving the figures from the authorities in Minsk, and the other by the visiting team confirming that they had seen 11 cases of childhood thyroid cancer in the clinic, and verified many more cases pathologically [1,2]. These were clearly aggressive thyroid carcinomas, with a high incidence of direct extra-thyroid invasion, lymph nodal and distant metastasis. The early excess was clearly in children, and by 10 years after the accident, 675 cases in children under 15 at operation had been reported from Belarus and northern Ukraine with the majority arising from the most heavily exposed oblast of Gomel [3]. Well over 1,000 cases of thyroid carcinoma had occurred by 1996, in those who were under 18 at the time of the accident rising to 1,800 by the year 1998. Nearly all the cases were papillary carcinomas.

The scale of the early increase was dramatic; in the mid 1990s, nearly 100 cases of childhood thyroid cancer a year were occurring in Belarus, a country with about two and a quarter million children. To put that into perspective, the world incidence of thyroid carcinoma in children under the age of 15 is of the order of 1/million/year and the recorded incidence in Belarus before Chernobyl was less than this. Some countries show an incidence of about 3/million/year, and some US registries 6/million/year. The number of cases continues to rise, the UNSCEAR review in the year 2000 quoted a figure of 1,800 cases in Belarus, the northern part of Ukraine, and the adjacent parts of the Russian Federation, while the 20 year review by WHO and IAEA gives a figure of 4,000 [3,4].

The immediate reaction from Europe and North America to the first reports of an increase in thyroid cancer 4 years after the accident was sceptical for various reasons. It was generally felt that radiation from $^{131}$I was much less carcinogenic to the thyroid than external radiation; indeed it was often assumed that it carried no significant risk for thyroid carcinogenesis in man. It was also assumed that the latent period for the development of thyroid carcinoma after radiation exposure was 10 years. These two reasons for scepticism about the reports were combined with uncertainty about the accuracy of the diagnosis: the knowledge that occult thyroid carcinoma of no clinical significance was a very common tumor, and experience of the extent of increased ascertainment that could follow greater surveillance. In retrospect, it can be seen that the scepticism was unjustified.

AGE-RELATED SENSITIVITY

The belief that $^{131}$I carried little carcinogenic risk was based on human and early animal studies. $^{131}$I had been used in the treatment of thyrotoxicosis for many years,

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**TABLE I. Relative Releases of Iodine-131**

<table>
<thead>
<tr>
<th>Year</th>
<th>Release Ci</th>
<th>Release Bq</th>
<th>Scale (Windscale units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Mile Island 1979</td>
<td>15</td>
<td>$5.6 \times 10^{11}$</td>
<td>0.00075</td>
</tr>
<tr>
<td>Hanford, green run 1949</td>
<td>$8 \times 10^3$</td>
<td>$3 \times 10^{14}$</td>
<td>0.4</td>
</tr>
<tr>
<td>Windscale 1957</td>
<td>$2 \times 10^4$</td>
<td>$7.4 \times 10^{14}$</td>
<td>1</td>
</tr>
<tr>
<td>Hanford 1945–47</td>
<td>$7 \times 10^4$</td>
<td>$2.6 \times 10^{16}$</td>
<td>35</td>
</tr>
<tr>
<td>Chernobyl 1986</td>
<td>$4.6 \times 10^7$</td>
<td>$1.7 \times 10^{18}$</td>
<td>2,300</td>
</tr>
<tr>
<td>Nevada 1951–62</td>
<td>$1.5 \times 10^6$</td>
<td>$5.6 \times 10^{18}$</td>
<td>7,500</td>
</tr>
</tbody>
</table>

Windscale nuclear accident, also involving a graphite fire as did Chernobyl, is arbitrarily set as one unit. Nevada refers to the releases from the above ground nuclear tests in that State.

**TABLE II. Distribution of Thyroid Doses With Age in Gomel Oblast in Belarus**

<table>
<thead>
<tr>
<th>Absorbed dose mGy</th>
<th>&lt;1 year</th>
<th>8–11 years</th>
<th>16–18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>0.7</td>
<td>8.4</td>
<td>16</td>
</tr>
<tr>
<td>5–100</td>
<td>2.9</td>
<td>6.5</td>
<td>9.4</td>
</tr>
<tr>
<td>100–300</td>
<td>11</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>300–1,000</td>
<td>30</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>1,000–2,000</td>
<td>16</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>&gt;2,000</td>
<td>34</td>
<td>10</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Data from Unscear 2000 [3].
and careful studies had shown that no subsequent carcinogenic risk could be detected [5]. However, almost all the patients treated were adults, and the Chernobyl-related carcinomas were developing in those exposed as children. In addition, the dose of $^{131}$I used in treatment was usually high enough to lead to cell death—and dead cells do not give rise to tumors. Thyroid follicular cells have a long intermitotic life, and cell death occurring at the subsequent division was the cause of the delayed hypothyroidism in these patients. Studies of the possible risk from the much smaller dose used in diagnostic studies with $^{131}$I, more often carried out in children although rarely in very young children, were more equivocal [6]. Early animal observations had seemed to lend support to the low carcinogenicity of $^{131}$I, finding that it was 10 times less likely to lead to thyroid tumors than external radiation. However, these were small studies, and a much larger study concluded that both types of radiation had approximately equal carcinogenicity [7]. Findings after the Chernobyl accident show that children under 1 year of age at exposure had developed 10 times as many thyroid tumors as those aged 10 at exposure by 11 years after the accident [8]. When the proportion of those that are likely to be spontaneous tumors is taken into account, the ratio will be much greater. The belief that Iodine 131 carried little or no carcinogenic risk in humans, still quoted in 1998 [6], was based on studies of exposures of adults, and was transferred unthinkingly to exposures of children.

An early analysis of the age distribution of post-Chernobyl thyroid tumors found that while the first group of cases showed a peak age of 7, 2 years later that had risen to 9, this quite clearly reflected an age-related sensitivity to the risk of thyroid carcinogenesis from exposure to fallout. Analysis showed that children less than 1 year of age were the most sensitive, with sensitivity falling with increasing age at exposure to relatively low levels [9]. Twenty years after the accident, children no longer show Chernobyl-related thyroid cancers, but those who were children at the time of the accident, now in their 20s continue to show an increased incidence. Early reports did not find an increase in the incidence of thyroid carcinomas in those who were adult at exposure, later studies have found a several fold increase, but increases have also been reported in non-exposed areas of the Russian Federation. The age at exposure has, therefore, been shown to be a critical factor in the risk of developing thyroid carcinoma after exposure to fallout from Chernobyl, with those under the age of 1 showing a very much greater risk than older children at exposure, with a rapid decline to a relatively low risk for young adults [8,9]. The likely reasons for this age-related risk include the intake of radioisotopes of iodine, the uptake of radioiodine, and biological sensitivity factors. Iodine intake is greater in young children because of the greater amount of milk in the child’s diet, and milk is the main route by which iodine isotopes from fallout are ingested. Children also have a higher thyroid uptake of radioactive iodine than adults. Studies from the Russian Federation found that after exposure to fallout, children under 1 showed a thyroid uptake of between 7- and 15-fold that in adults [3]. (Table III) The existence of biological sensitivity factors is shown by the finding of similar although less marked age-related sensitivity to thyroid carcinomas after exposure to external radiation [10].

Two main reasons for this sensitivity could be either the mitotic rate at the time of radiation exposure, or the number of mitoses that occur in the progeny of the mutated cell, or both. As most point mutations occur during S phase, the mitotic rate at exposure is likely to be important for oncogenes activated in this way. The situation for rearrangement is more complex; it has been shown for some RET rearrangements that the breakpoints lie very close together in the interphase nucleus [11], suggesting that this is when the rearrangement occurs. Radiation is particularly effective at producing double strand breaks in DNA, the necessary precursor to rearrangements. As the initial rearrangement is almost certainly not sufficient to give a clinically significant cancer, further mutations are likely to be needed. In the absence of further radiation, these are likely to be point mutations; under these circumstances, the number of mitoses in the clone derived from the mutated cell will influence the risk of development of clinically significant cancer. In the thyroid, the mitotic rate drops with age to reach very low levels in adult life [12], the number of mitoses in the clone derived from the mutated cell drops even more rapidly with the age at exposure.

The sensitivity of very young children to thyroid carcinogenesis after fallout exposure has important implications for future nuclear accidents.

**LATENCY**

The presumed latent period of 10 years for radiation induction of thyroid carcinoma was not derived from atomic bomb studies, but from the follow-up of children

<table>
<thead>
<tr>
<th>Age</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>1–2</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>3–7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>8–12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>13–17</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;17</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data from Unscear 2000 [3].
treated with external radiation to the neck area. This figure, quoted in the 1990 IAEA report on the effects of Chernobyl, was based on studies of several thousand children, for example, the Rochester study of about 2,500 children exposed to X-rays for presumed thymic enlargement, with the subsequent development of 33 thyroid cancers [13]. In contrast, about 2 million children were exposed to varying levels of fallout in Belarus alone, and by 18 years after the accident, over 2,000 cases of thyroid cancer had occurred in that country [14]. A later meta-analysis combined several reports of thyroid carcinoma induced by external radiation of children, and concluded that although two cases had occurred within 5 years of the exposure, this was not significant, but there was a significant risk 5–9 years after exposure [10]. Analysis of the data in this report showed that 20% of the cancers that had occurred by 20 years after exposure were found before 10 years and 2% before 5 years; in Belarus, the figures are approximately 17.5 and 3%. While the Belarus data is approximate partly because data are provided per calendar year, the difference in scale could account for the apparent early detection of an increase. Scepticism over the reports of increases in thyroid cancer incidence only 4 years after exposure were based on the assumption that a latent period should be regarded as fixed, an idea that is difficult to sustain on biological principles. The simple explanation is that the larger the size of an outbreak, the earlier it becomes possible to detect the first increase. As has been pointed out, the thyroid carcinomas that have already followed the Chernobyl accident form the largest number of tumors of one type due to one cause on one date that has ever occurred [15]. Because the main isotope was $^{131}$I, with a physical half-life of 8.1 days, we know that the first event in the carcinogenesis cascade almost certainly occurred within a few weeks after April 26th, 1986 allowing the latent period to be accurately determined. It is, therefore, possible to correlate latency with changes in tumor morphology, aggressiveness, and molecular pathology [16].

**TUMOR MORPHOLOGY AND AGGRESSIVENESS**

Virtually, all the thyroid carcinomas were papillary in type. The early cases showed a high proportion of the solid variant of papillary carcinoma, later cases showed an increasing proportion of more classical papillary carcinomas. The early cases were also often aggressive locally invasive cancers with a high proportion of distant metastasis. This aggressiveness has not been a feature of the majority of later tumors. These changes could be related to changes in latency, or simply to changes in age at operation, as these two variables are strongly correlated. A study comparing groups of tumors with different ages at exposure, but the same latency and the same age at operation shows clearly that latency is the important factor [16]. Concerns that had been expressed about the accuracy of the diagnosis were unjustified; review of cases in the major centers of Minsk and Kiev showed a very high degree of agreement on the diagnosis. The problems of ascertainment were not relevant in the early cases which almost all presented clinically, and certainly did not have the characteristics of occult carcinomas. As the exposed population ages, the numbers of spontaneous cases is increasing, and with increasing awareness of the problem and more sophisticated screening, greater ascertainment must be relevant.

**MOLECULAR FINDINGS**

In sporadic papillary carcinomas in adults, the great majority of cases show either a rearrangement in the RET oncogene or a point mutation in the BRAF oncogene, with little or no overlap [17]. In the Chernobyl-related thyroid carcinomas, (so far virtually all papillary carcinomas), studies of the early cases showed a very high proportion with RET PTC3 rearrangements [18]. Over time, the proportion with RET rearrangements has declined, but RET PTC1 rearrangements have formed a higher proportion of these [19]. BRAF mutations have occurred at a low frequency in Chernobyl-related thyroid carcinomas, but they are also infrequent in thyroid carcinomas in non-exposed children [20]. It cannot, therefore, be assumed that they are not radiation related, as they could be associated with a longer latent period. There are, however, several reasons why at present it seems less likely that they are due to radiation than RET rearrangements. The main reason is that radiation is generally accepted to be more likely to be associated with double strand breaks than point mutations. Also several in vitro studies suggest that the type of mutation that activates BRAF, a T → A transversion is one of the least likely of the point mutations to be induced by radiation. Other evidence comes from a study of thyroid carcinoma after external radiation in childhood; even in adult life, the tumors are found to show a low proportion of BRAF mutations [21]. It is also of interest that BRAF is a key gene in malignant melanoma, and unlike other skin tumors, malignant melanoma did not increase in frequency after the atomic bomb exposure [22]. It is also worth noting that one case of BRAF activated by rearrangement has been found in a child with a post-Chernobyl papillary carcinoma [23].

**GENERAL POINTS**

It is now possible to put together a coherent picture of the development of thyroid carcinoma in those exposed to
fallout from the Chernobyl accident [15,16]. The main source of the radiation to the thyroid was $^{131}$I in the fallout, and this led to DNA double strand breaks, and probably some point mutations. Double strand breaks that led to RET rearrangement were able after the acquisition of additional mutations to lead to papillary carcinoma of the thyroid. RET PCT3 rearrangement gave rise to more rapidly growing tumors that were clinically more aggressive, with a shorter latent period and, a less mature more solid morphology. RET PCT1 rearrangement gave rise to less rapidly growing tumors with a longer latent period, a more mature classic papillary morphology and less aggressive clinical behavior. BRAF mutations have been found in only a minority of the post Chernobyl papillary carcinomas, and while these could have been radiation induced, it must be remembered that with increasing time since the accident, the proportion of spontaneous cases will be increasing among the exposed population. This is particularly the case in those who were older at the time of the accident. In a significant proportion of cases, neither rearrangements nor BRAF mutations have been found, showing that other as yet unknown mutations are involved. Interestingly, despite all the differences between the two events, estimates of the excess relative risk per Gy for thyroid carcinoma after Chernobyl are broadly similar to those derived from the atomic bomb and other external radiation studies [24].

One feature that is relevant to some of the findings in the occurrence of thyroid carcinoma after exposure to fallout from Chernobyl is that much of the area where the fallout occurred is iodine deficient. Iodine-deficient thyroid glands will of course show a high uptake of radioactive iodine, leading to the prediction that the risk of developing thyroid carcinoma after exposure to radiation would be greater in areas with greater iodine deficiency. This has been shown after Chernobyl, with major differences in the ERR/Gy between high and low iodine areas [24]. This important observation is yet another reason for I supplementation in areas of deficiency. It also seems likely that longer term iodine supplementation after the accident significantly reduced the risk [24] (Table IV). Animal studies have shown that thyroxine treatment after radiation exposure can abolish subsequent thyroid tumor formation [25].

The present report does not set out to deal with the treatment of the thyroid cancers, but it is worth commenting that some of the early aggressive cases were treated by hemi- rather than total-thyroidectomy; one of the reasons for this was that at the time, adequate supplies of thyroxine were not available to treat hypothyroidism.

After an accident which releases a large amount of radioactive iodine, the standard advice to the population which may be exposed is to shelter, to avoid milk and other foodstuffs from the fallout area, and, for those under 40, to take stable iodine (or iodate in some countries). For stable iodine to be effective, it must be taken shortly before or within a few hours of exposure. Because of the time delay between the accident and the occurrence of fallout this is feasible, but may require predistribution of the tablets. After Chernobyl, very few had access to stable iodine, and information about the accident was delayed, so that the population in general continued to drink local milk. There are many problems in managing the consequences of a nuclear accident, including public panic which may lead to overcrowding of the roads and obstruct action to deal with the accident. However, there is little doubt that if immediate advice had been given, many of the cases of thyroid carcinoma, probably the majority, would not have occurred. While advances in nuclear technology mean that modern reactors, which do not have a flammable graphite core, and which possess secondary containment are very much less likely to give rise to an accident with releases like those from Chernobyl, such an event cannot be completely discounted, and many lessons can be learnt from the events surrounding the Chernobyl accident and its consequences.

**THE FUTURE**

A number of challenges remain for the future study of the consequences of the Chernobyl accident. It is important to continue to document the thyroid cancers, to study the morphological types, the molecular pathology findings, and the clinical behavior, so that these can be correlated with latency. It is important also to estimate how much of the increase is due to increased surveillance, so that the numbers of carcinomas occurring in those at risk can be divided into the cases due to radiation, the normal incidence, and the proportion of each that are due to increased surveillance. Thyroid carcinomas are associated with a particular problem in relation to surveillance,

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**TABLE IV. Excess Relative Risk for Thyroid Carcinoma, Comparing Chernobyl to External Radiation, and Comparing the Effect of Iodine Intake on the Risk**

<table>
<thead>
<tr>
<th></th>
<th>Chernobyl overall</th>
<th>External radiation</th>
<th>Chernobyl high iodine</th>
<th>Chernobyl low iodine</th>
<th>Chernobyl high I + KI</th>
<th>Chernobyl low I + KI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERR at 1 Gy</td>
<td>4.5–7.4</td>
<td>7.7</td>
<td>2.5</td>
<td>9.8</td>
<td>0.1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Data from Cardis et al. [24].

*Journal of Surgical Oncology DOI 10.1002/jso*
the frequency of occurrence of papillary microcarcinomas and the increased sensitivity of ultrasound investigation allowing the detection of lesions a few millimeters across. There seems little doubt that the great majority of cases that occurred in those who were children both at exposure and at the time of operation were due to radiation, but it also seems likely that for those who were 17 or 18 at the time of the accident, a high, and possibly very high, proportion of the cases will be due to non-Chernobyl causes, together with increased surveillance. The present position is that about 4,000 thyroid cancers have occurred in those who were under 18 when exposed to fallout in Belarus, Ukraine, and exposed oblasts of the Russian Federation [4]. Over half of these have occurred in Belarus, and the frequency of occurrence has been linked to the level of exposure. Analysis of the data on thyroid carcinomas after external exposure [10] shows that by 20 years after exposure, only about 25% of the number of thyroid carcinomas that were found after 40+ years had occurred. If the Chernobyl outbreak follows the same temporal pattern, the eventual number of thyroid carcinomas would be over 12,000. Fortunately, differentiated thyroid carcinoma is an eminently treatable condition, and to date only 15 deaths have been recorded. This is clearly not the final figure; although 4,000 cases are quoted, the majority were first treated less than 10 years ago, so that more deaths may occur in these as well as future cases. Pulmonary fibrosis has occurred in some treated cases with lung metastases. Nevertheless, the total number who will die from thyroid cancer will hopefully be no more than 5% of all cases. It may well be much less if the future tumors with longer latency continue to show the classic features of papillary carcinoma and continue to show only a small population of RET PTC3 or BRAF-positive cases. It is not possible to predict the eventual future death rate with any certainty, because of the possible future occurrence of different tumor types. If the reduction in aggressiveness with increasing latency continues, the overall death rate for the post radiation thyroid carcinomas, currently 15 out of about 4,000 cases [4], is likely to be very low, particularly as papillary carcinomas with RET rearrangements seem less likely to progress to undifferentiated carcinoma than papillary carcinomas with BRAF mutations. However, it remains possible that papillary carcinoma with BRAF or other mutations may occur in the future, and also that follicular, medullary, or undifferentiated carcinomas may occur. Follicular carcinomas are known to be associated with radiation, although to a lesser extent than papillary carcinomas, and probably with a longer latent period.

As well as the deaths from thyroid cancer, the consequences of the accident include the morbidity associated with thyroid disease, with many more than 4,000 thyroidectomies, with associated complications, and many more in the future. It seems likely that thyroid adenomas are also becoming more common; these are known to increase in frequency after radiation, but with a long latency [26]. Dramatic as the thyroid consequences are, they have affected many fewer people than the psychological consequences, due to the fear of the possible effects of radiation, together with for many families, the upheaval of evacuation from contaminated areas. The total cost of the clean up operation has been enormous, and has increased the poverty of an already poor area, particularly in Belarus, the most affected country even though the reactor was outside its borders.

Finally, we should be careful to ensure that the dramatic increase in thyroid cancer does not distract attention from the need to study all other possible effects of radiation from fallout. Studies comparable to the comprehensive studies that have been carried out after the atomic bomb are needed. Twenty years after the atomic bomb exposure, the only statistically significant increases in cancer seen in the survivors were in leukemia and thyroid carcinoma. The continuing studies later found significant increases in a wide range of malignant and non-malignant conditions. While it seems unlikely that there will be any comparable findings after Chernobyl, if careful studies are not undertaken, inappropriate claims, exaggerating or downplaying the consequences will continue to be made.

REFERENCES


