New insight into cancer risks from radiation exposure of low dose and low dose rate

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It is well known that carcinogenic effects of ionizing radiation are late effects. These late effects are considered as stochastic events that occur with a *probability* that depends on radiation dose.

Slide 2

Estimation of radiation cancer risks generally signifies evaluating the *probability* of stochastic late effects.

Carcinogenic late effects do not have any unique feature associated with the involvement of radiation in their etiology. That is why carcinogenic effects of ionizing radiation can only be revealed statistically as increased rates associated with radiation dose in studies of groups of persons with varying exposure.

Estimations of cancer risks are based upon epidemiological studies of groups of people or even populations exposed to ionizing radiation. They include the atomic bomb survivors, persons exposed medically or occupationally and populations exposed environmentally and others.

Risk estimation involves not only estimation of a *risk coefficient* (e. g., relative risk- RR), but also requires accounting for spontaneous (background) rates of disease or death and assessment of effect modification by age of exposure, time, gender, attained age and other factors. The most common risk model is the excess relative risk (ERR) model. The simplest ERR model is linear ERR model.

Biological effects of intermediate and high doses of Ionizing radiation, say above 100 mSv, are studied rather well. The risks of low-dose radiation are of high social importance due to health effects of occupational and environmental exposure, the future of nuclear power and others, but at low radiation doses the situation is much less clear in comparison with high dose range.

Slide 3

For example, the Chernobyl accident caused the deposition of radioisotopes over wide areas of the Northern Hemisphere, in particular in Europe (Atlas of Caesium Deposition on Europe after the Chernobyl Accident, 1998), followed by protracted chronic exposure of some millions of people to external and internal radiation. You can see the map of radioactive contamination of Europe after the Chernobyl accident that took place in 1986.

For the time being the scientific community considers low dose exposure as 100 mSv and less.

As to concerning radiation doses due to Chernobyl catastrophe, populations of the three most affected countries such as Republic of Belarus, Ukraine and the most contaminated regions of Russian Federation ware exposed to low-dose ionizing radiation with low dose rate and received life-time cumulative mean effective doses in the range of 10 – 100 mSv.

So, the most accurate estimates of the whole body absorbed doses for country inhabitants of Bryansk region of Russia over the period from 1990 to 2000 years are reported in the joint Nordic- Russian project (Thornberg et al., 2005). Initial contamination levels of ^{137}Cs were between 0.9 and 2.7 MBq m^{-2}. The external irradiation was determined during 1 month in Septemner-October each year, using thermoluminescent dosimeters. The mean effective dose from external and internal irradiation due to $^{137, 134}Cs$ deposition varied between 2.5 and 1.2 mSv per year between 1990 and 2000. The contribution from the internal dose to the total mean effective dose was 30-50%, depending on the village. The cumulated mean effective dose over the 70 years following the accident was estimated to be about 90 mSv, reaching 500 mSv in some inhabitants of Bryansk region.

Slide 4

So far, the Life Span Study (LSS) cohort of Hiroshima and Nagasaki atomic bomb survivors is a major source of epidemiological data used for radiation risk assessment and for establishing radiation protection standards.

Let’s give a characteristic of the LSS cohort that was formed 5 years after bombings and included 120 321 persons who survive by that time (Preston et al., 2007).

The LSS comprised a basically healthy general population, including males and females, exposed to a wide range of radiation doses at all ages.

The main aspect of the LSS cohort that is often neglected is the highly skewed dose distribution and the large number of survivors who received low dose, although at high dose rate, exposure.

You can see that survivors with dose above 1Gy comprise less than 3% of the cohort.

From the total number of persons in the LSS cohort (120 321 persons) about 35, 000 received doses between 5 and 200 mGy.

In fact, they comprise about 75% of the cohort members with dose above 5 mGy

In the whole LSS cohort of 120,321 individuals about 48% were still alive at the end of 1998.

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The Life Span Study cohort of atomic bomb survivors are often considered as the high-dose study. But, in reality, the mean dose in the exposed group in the whole cohort is only 200 mSv, with above 50 % of affected individuals in the cohort (26 300) taking dose below 50 мSv (Preston et al., 2003).

Let’s consider time course of recorded carcinogenic effects in the LSS cohort. Only significant increases in leukemia and thyroid cancer were important consequences of irradiation 20 years after bombardments. However, in 1974, a significant increase in solid cancers, other than thyroid cancer, was revealed among survivors with dose above 1 Gy. But they comprise less than 3% of the cohort.

In 1994, in 40 years after bombardments, the first complete report was published. It was in the form of 4 articles on cancer incidence among the cohort members over the period from 1958 to 1987. One has to remind that tumour register was

compiled in 1958. That is why cancer incidence could not be evaluated for the first 13 years after the bombings.

The analysis of the mortality from cancer diseases in the atomic bomb survivors over the period of 1950–1990, i. e. over 40 years of follow up, revealed the statistically significant radiation effects beginning from 0.2Sv (200 mSv or 20 rem) (Pierse et al., 1996).

In 2000, Pierce and Preston evaluated solid cancer incidence for the period of 1958 through 1994 focusing on the subcohort of about 50,000 LSS survivors who received dose less than 0.5 Gy to clarify cancer risks at low doses. This large group of low- to moderate- dose survivors provides adequate statistical power to make direct evaluation of cancer risks at low doses.

They concluded there was a statistically significant dose response in the range of 0–0.15 Gy.

The atomic bomb survivors in the dose range from 5 to 100 mSv show a significantly increased incidence of solid cancer compared with the population who was exposed to less than 5 mSv.

This conclusion was confirmed by the second general report on radiation effects on the incidence of solid cancers among members of the LSS cohort of atomic bomb survivors (Preston et al., 2007). The data you can see on this slide

Analysis was based on more than 40 years of cancer incidence data for the members of the LSS.
34% of the cancers included in the current analysis were diagnosed during 1988-1998.
It was estimated that about 11 % of the cases among cohort members with colon dose in excess of 0.005 Gy were associated with atomic bomb radiation exposure.

The authors write "there is a statistically significant dose response when analysis was limited to cohort members with doses of 0.15Gy or less".
This report provides further evidence that radiation-associated increases in cancer rates persist throughout life regardless of age of exposure.

The history of studies carried out on the basis of atomic bomb survivors clearly demonstrates that malignant neoplasms induced by low doses have quite long latency.

Slide 6

There are many difficulties involved in quantifying the risks of low-dose radiation.

The first problem is the very large studies are required to assess the risks of very low dose of Ionizing radiation.

As usually, the studies of low doses do not provide adequate statistical power, so results from exposure to high dose must be extrapolated to low dose range with appropriate adjustment for other differences.

The study of groups of survivors in the LSS cohort including only doses below 0.1 Gy do not have enough attributable fraction to give meaningful estimate, and

such study produces results that depend on the choice of unexposed comparison group.

This slide show risk estimates for solid cancer mortality among groups of survivors, who were exposed to low dose, below 500 mSv. The first two data points (in blue) with mean dose 20 and 29 mSv are not statistically significant as compared with the population exposed to below 5 mSv. The remaining four higher dose points are statistically significant (Brenner et al., 2003).

But in general the persons in the dose category from 5 to 125 mSv (the mean dose for this group consists of 34 mSv) show significant increase in cancer mortality.

The second difficulty of assessment of low dose risks is a shape of dose response relation.

The cancer dose response relationship is usually assumed to be linear without of a threshold. It is so-called linear no – threshold assumption.

This assumption has recently received new scientific support in BEIR VII – Phase 2 (2006) and has been corroborated in recent study of Cardis et al on estimates of radiation-related cancer risks among radiation workers in the nuclear industry (Cardis at al., 2007)

A large amount of data are available, both from epidemiological and laboratory study, that are consistent with a linear dose-response relationship. But evidence for the presence of downward curving (decreasing slope) dose-response relations, both from epidemiological and laboratory studies, also exists for low dose range.

You can see on this slide that the most recent low dose atomic bomb survivor data for cancer mortality appear to exhibit such shape (Brenner et al., 2003).

Slide 7

The recent low-dose atomic bomb survivor data for cancer incidence (Pierce, Preston, 2000) also exhibit such shape of dose-response curve. On this slide you can see downward dose-response relations at low dose range in comparison with the full dose range.

Possible different shape of dose response relations in the low dose range, first of all downward curving dose response, is a great challenge for radiation risk estimation. From practical point of view it is important that downward curving dose response means the following.

The estimated excess relative risk (ERR) per Sv at the low dose ranges of the Life Span Study cohort might be the highest for the lowest dose category, namely from 0.005 to 20 mSv in comparison with the dose range between 0 and 3 Sv (Pierse et al., 1996).

Of course, the shape of the dose response curve at such low doses cannot be unequivocally established through epidemiological studies.

Nevertheless some recent publications give some preliminary evidence that radiation risk per unit of dose may be higher at the low dose range in comparison with higher doses.

In summary, carcinogenic effects of low-dose ionizing radiation were demonstrated in the rage of 0.005 – 0.15 Gy for the LSS cohort of Hirosima and Nagasaki atomic bomb survivors who received acute exposure over a very short period.

Carcinogenic effects of so low doses were recorded within 40 years following exposure.

But in majority of cases exposed persons irradiated with low doses, such as occupational or fractionated exposure, environmental exposure due to radiation accidents.

For example, after the Chernobyl fallout affected populations were exposed to relatively high dose rate over days or weeks followed by long lasting exposure to low dose rate over some decades.

For prognosis of both cancer incidence and mortality of chronically exposed populations, the International Commission for Radiation Protection and BEIR VII Phase 2 (2006) suggest to use radiation risks modified with the Dose and Dose Rate Effectiveness Factor (DDREF) under prolonged or chronic exposure with low dose rate. A direct effect of dose rate means that radiation risk decreases with reduction in dose rate.

David Brenner and coworkers reviewed recent information concerning cancer risks attributable to low doses of ionizing radiation. The article was published at PNAS in 2003. They made the following conclusion. The lowest dose of ionizing radiation for which good evidence exists of increased cancer risks in human is approximately 10 – 50 mSv for an acute exposure and approximately 50 – 100 mSv for a protracted exposure.

In general, chronic exposure to low LET radiation is associated with lower risks than those of an acute exposure to the same dose, both for cancer and other endpoints.

But at present there are a number of reports indicating that radiation risks of low dose rate radiation exposure of general populations may be higher than radiation risks established for survivors of LSS cohort.

Slide 8

A recent study of solid cancer mortality in the Semipalatinsk historical cohort whose members were suffering from Soviet atmospheric nuclear weapons testing in Kazakhstan concerned health effects of fallouts exposure over a period of 40 years (Bauer et al., 2005). This European Commission-funded study has been conducted in collaboration with the Republic of Kazakhstan. An exposed group consisted of residents of the highly exposed villages whereas the comparison group consisted of residents of the villages distant from the Semipalatinsk nuclear test site with a collective dose estimate of 20 mSv due to multiple fallouts. The total cohort included both the exposed group and the comparison group. The members of the total cohort received acute external and chronic internal exposure due to radionuclide intake. Individual dose estimation has been calculated using the Techa River Dosimetry Systems 2000 developed over 10 years.

Cumulative effective radiation dose estimates in the total cohort ranged from 20 mSv to about 4 Sv. A significant association between solid cancer and radiation dose was found in the Semipalatinsk historical cohort.

The risk estimate per unit of dose for all solid cancers was 1.77 (95%CI from 1.35 to 2.27) based on the data for the total cohort. This is 4-times higher than the radiation risk of mortality from solid cancers of atomic bomb survivors. The ERR/Sv based on the exposed group was 0.81 (0.46; 1.33) for all solid cancers

combined and thus still exceeded current risk estimates from the Life Span Study cohort. The point estimate of the ERR/Sv for all solid tumours of the Semipalatinsk exposed group was outside the range of the confidence intervals of the LSS cohort.

At present, the Techa River cohort and the 15-country collaborative study of nuclear industry workers are the largest and most informative radio-epidemiological studies of the effect of protracted low-dose rate exposures to ionising radiation.

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It is clear that assessment of radiation risks in workers exposed to ionizing radiation in the course of their work attracts great attention now. So, International Agency for Research on Cancer has recently co-ordinated a combined study of mortality and external radiation exposure in nuclear workers from 15 countries (Cardis et al, 2007)..

This slide presents ERR of cancer mortality of the National Register of Radiation Workers in Great Britain and the joint cohort of International Agency for Research on Cancer as against the LSS cohort (Muirhead et al., 2008). The total studied population of 15 countries consisted of about 400, 000 workers. Most of the workers were men (90%), and the average lifetime dose was about 19 mSv (Cardis et al, 2007). A very important characteristic of such radiation cohorts is strong "Healthy Worker Effect" (HWE), i.e. lower overall mortality compared with national rates. However, cancers could occur in such healthy workers.

Thus, for all tumors excluding leukaemia and lung cancer, risks were greater than four times risk estimates in the A-bomb survivors. However, the confidence intervals from the three studies overlap.

The recent multi-country study reveals that there is an increase in cancer risks even at the low doses and dose-rate usually received by nuclear industry workers.

So the lowest dose of chronic radiation exposure for which good evidence exists of increased cancer risk in human is approximately 19 mSv. Earlier Brenner and coworkers suggested that such lowest dose is in the range of 50 – 100 mSv.

Slide 10

The members of the Techa River cohort received protracted exposures, both external and internal at low-dose rates. They were followed up over 1956 – 2002 (follow – up time was 47 years).

The excessive relative risk of solid cancer mortality in the Techa River cohort proved to be approximately 0.92/Gy (Krestinina et al., 2005). This value can be expressed as 1.3/Sv by using equivalent absorbed dose. The last velue is 3-times higher than excessive relative risk of 0.42/Sv for solid cancer mortality established for atomic bomb survivors for gender-average estimate.

Like the mortality data, the report on cancer incidence in the Techa River cohort (Krestinina et al., 2007) provides clear evidence of increase in solid cancer rates and a strong dose-response relationship associated with exposure to radiation from the contaminated Techa River. The ERR for solid cancer incidence was 1.0 /Gy in a linear dose-response model. However estimates of the long term health

risk associated with chronic exposure must be interpreted with caution because of some uncertainties in the dose calculation.
The risk estimates for the cancer mortality and cancer incidence in the Techa River cohort were almost identical: 0.92/Gy for mortality and 1.0 / Gy for cancer incidence and were higher than those for the LSS cohort.
It is worthy to note that solid cancer risk estimates derived from studies in the Techa river population are compatible with the ERR/Sv of 0.81 (0.46; 1.33) derived from the Semipalatinsk cohort's exposed group.

The estimated ERR of mortality from solid cancers in Russian clean-up workers determined by Russian scientists (Ivanov et al., 2006) and radiation risk estimates of some cancer sites made by Mikhal Malko and co-workers (Malko et al., 2006) in the population of Belarus were more higher than those in the LSS cohort. The results of these studies are in line with those of the above–listed low dose cohort studies. But dose rates of liquidators were approximately $3 \cdot 10^{12}$ times less than dose rates of atomic bomb survivors.

The estimates of ERR of solid cancer mortality in the unselected general population of the Techa River (1.0/Gy) is practically the same as that (0.9/Gy) of mortality in the pooled cohort of nuclear workers.

Unfortunately these studies have some limitations and precise values of cancer risks in such low- dose cohorts will be determined in future.
Taking together these large epidemiological studies give strong evidence on cancer risks attributable to protracted low dose delivered with low dose rate.

At this time the data of the Techa River cohort and the Semipalatinsk historical cohort, like the pooled nuclear Study data, do not provide any evidence to support the widespread opinion that low dose rate protracted exposures are less effective (per unit of dose) than acute exposures with high dose rate.

Of course, it is a great challenge to current radiation protection recommendation such as given by International Commission on Radiological Protection (ICRP) and BEIR VII Phase 2 (2006).

Meanwhile, this is good verification that radiation risks in the Life Span Study cohort and especially use of Dose And Dose Rate Effectiveness Factor (DDREF) are not applicable for assessment of expected increase of cancer mortality and cancer incidence for general populations irradiated at low dose and low dose rate.

Cardis and coworkers made estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident using cancer risks of the BEIR VII model and the dose and dose – rate effectiveness factor (DDREF) of 1.5 (Cardis et al., 2006). However analysis of current data on the problem of cancer risk at low doses shows that their values of cancer burden might be underestimated.

Conclusions

Doses of the whole body irradiation of affected populations of the Republic of Belarus, Ukraine and contaminated regions of the Russian Federation are in the dose range of 0.005–0.15 Gy, i. e. within the range of doses that caused statistically significant increase in cancer incidence in the Life Span Study cohort of atomic bomb survivors.

There is an increasing set of data showing that radiation risks of chronic irradiation of populations at low doses and low dose rates may be higher than radiation risks in the LSS cohort.

The 15-country collaborative study of cancer risk among radiation workers of the nuclear industry give evidence that excess relative risks (ERR) of all malignant neoplasm excluding leukemia and lung cancer is approximately 3 times higher than radiation risk in the LSS cohort.

The results of some studies do not suggest that cancer risks associated with low-dose rate exposure are less than those in LSS cohort exposed acute irradiation at high dose rate

Thus, cancer risks in the LSS cohort and especially use of Dose and Dose Rate Effectiveness Factor (DDREF) higher than 1 are not applicable for prognosis estimates of radiation induced cancers in the case of long – term radiation exposure of populations to low dose rate such as Chernobyl fallout exposure

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