



Effect of Radiation Exposures on Fetal Hematopoietic Cells

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Abstract

Purpose of this Review It has generally been thought that fetuses are highly sensitive to radiation-induced cancer. Epidemiologic case-control studies indicated that X-ray exposures given to pregnant women (on the order of 1 cGy) could have increased the risk of developing childhood leukemia and solid cancers in the offspring. The authors wished to re-consider this observation.

Recent Findings Atomic bomb survivors who were exposed in utero were found to show almost no increase in the frequency of translocations in their blood lymphocytes when the survivors were examined at around 40 years of age. Subsequent animal studies revealed that tissue stem cells in embryos/fetuses may or may not retain radiation-induced chromosome damage depending on the developmental stage at the time of irradiation.

Summary Our data are compatible with the model that radiation effects can be recorded only when an exposure occurs after the stem cells have settled in their appropriate niche, and that a small fraction of fetal hematopoietic stem cells began making long-term contributions to the lymphoid cell pool in both mice and humans. It remains to be established whether or not the increased risk of childhood leukemia and other childhood cancers was caused by fetal X-ray exposures of about 1 cGy.

Keywords Chromosome aberrations · Fetal irradiation · Hematopoietic stem cells · Childhood leukemia · Atomic bomb survivors

Introduction

It is generally believed that developing organisms in utero are highly sensitive to radiation exposures. This notion is derived from two observations: one is that fetal exposures to radiation may cause congenital malformations which do not develop after postnatal exposures. The other observation is that fetal exposures may cause childhood cancers (especially childhood leukemia), which was first described in an epidemiologic study called the Oxford Survey of Childhood Cancers (OSCC) [1–3]. In England and Wales from 1920 to 1960, the mortality rate for childhood leukemia kept increasing, and a large amount of attention was focused on the etiology of the disease. The OSCC survey was begun under these circumstances, and was a case-control study of childhood

leukemia and other cancers. It consisted of identifying children who died from childhood cancer (leukemia and solid cancers) before the age of 10 years or later (the cases), and also followed children who did not die from cancer (the controls) who were matched by birth year, location, and sex. The mothers were subsequently interviewed to identify factors which could reveal significant differences between the two groups. The study found that the proportion of mothers who had X-ray images taken in the abdominal region during pregnancy was significantly higher among the cases (about 13~15%) when compared with the controls (10%) but this was not found in the case of other, non-abdominal, X-rays. The difference in the frequency of abdominal X-rays permitted the investigators to estimate that there was an odds ratio (approximating the relative risk, or RR) of 1.3 to 1.5 for childhood cancer (both leukemia and other cancers). Because the X-ray doses at that time were estimated to be about 1 cGy per film, the risk after a 1-Gy exposure can be 100 times the risk for a 1-cGy exposure, i.e., RR per Gy may reach a value as high as 30 to 50 if a linear dose response is assumed. The estimate is unusually large when compared with the RR of about 1.5 per Gy for solid cancers in those who were exposed to radiation at the age 30 years and reached the age 70 years [4, 5]. On the other hand, this large RR is not unprecedented

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but is similar to that found for leukemia among those who were exposed to the atomic bomb's (A-bomb) radiation in their early childhood [6••].

Subsequently, similar case-control studies were undertaken in various locations around the world. The results were generally similar and consistent with those of the OSCC survey [7]. Because the reproducibility was so good for small risks (with RR values of around 1.5 or a 50% increased risk), it appeared as if the relationship between abdominal X-ray exposures during pregnancy and the subsequent cancer risk for the offspring was firmly established. However, because the OSCC survey and other related studies are case-control studies (i.e., retrospective studies), the results suggest that there is an association between fetal exposures to X-rays and the subsequent risks for childhood cancer, but do not prove a causal relationship. In principle, prospective studies (i.e., cohort studies) were needed to prove a causal relationship, but some attempts to do this were not conclusive (see Table 6 of reference [8], and [9]). This is because childhood leukemia is a rare disease, so these studies require a large cohort in order to have sufficient statistical power.

Emerging questions

Overall, a question remains: how is it possible that there is a similar RR, not only between different types of leukemia, but also for leukemia and solid cancers in different organs [10]. These unresolved issues resulted in researchers falling into two groups: those either being affirmative of, or conversely suspicious of, these results (see references [8, 10, 11••] and for comparisons of specific opposing viewpoints, and a discussion in reference [12••] for an additional argument).

Following the OSCC survey and other related studies, the studies of A-bomb survivors exposed in utero gained attention because the radiation doses from the bomb were much higher than diagnostic X-ray doses. However, the results did not show evidence for an outbreak of childhood leukemia or solid cancers [13]. This lack of evidence is now thought to be due to the small number of study subjects (about 3000), and does not necessarily contradict the results of the OSCC study. Indeed, in the survivor study, highly elevated RR values for developing childhood leukemia are observed following childhood exposures [6••], which can be regarded as supportive of the causal hypothesis provided

that fetal lymphoid stem cells can somehow remain radiosensitive up until childhood. However, that scenario does not fit childhood solid cancers because highly elevated risks were seen only in case-control studies for fetal exposures but not in the survivor studies of childhood exposures [13]. Table 1 summarizes these contradictory results. Subsequently, in 2004, it was found that people who were exposed to A-bomb radiation in utero did not show evidence of radiation effects in their blood lymphocytes, although their mothers did [14].

Before describing the main focus of this discussion, it may be worth describing the basic characteristics of childhood leukemia (primarily acute lymphoblastic leukemia or ALL). This is a curious disease which has its peak onset at the ages of 2 to 5 years. In many instances, leukemia-specific translocations are already present at birth, but at a frequency 100 times higher than that of the actual incidence of the disease [16, 17]. This means that only a small fraction, i.e., 1% of the translocation carriers, develop ALL later in life. Furthermore, the early peak for the onset is seen in developed countries but not in developing countries [18, 19]. It has been suggested that some types of infections are involved in the etiology of the disease [20, 21]. Therefore, it seems that the monotonically increasing trend of childhood leukemia seen in England and Wales when the OSCC study was conducted could possibly be attributed to improving hygiene which has started since the 1920s, and not due to increasing levels of pollution involving mutagenic or carcinogenic agents.

The Lack of Evidence for Cytogenetic Damage in A-Bomb Survivors Exposed In Utero

In the 1960s, the discovery of hemagglutinin (a mitogen) made it possible to culture blood lymphocytes and observe mitotic cell divisions. Those cells were previously believed to be terminally differentiated and unable to undergo additional cell divisions. This new technology permitted investigators to estimate radiation doses retrospectively by using chromosome aberration frequencies as a quantitative biomarker. In A-bomb survivors, individual radiation doses were estimated principally by using information such as the distance from the hypocenter, the structure of the survivor's house, and the survivor's location in a house (i.e., by using physical factors to

Table 1 Summary of the risks for leukemia and solid cancers following radiation exposure in utero or after birth

Study	Exposed as	Evidence for elevated risks			Reference
		Childhood leukemia	Childhood solid cancers	Adult-onset cancer	
Oxford Survey of Childhood Cancer	Fetuses	+	+	Unknown	[1–3]
A-bomb survivors	Fetuses	–	–	+	[13, 15]
	Children	+	–	+	

generate the exposure estimates). Estimating the biological doses by using chromosome aberration data was thought to be helpful in leading to a better understanding of any possible biases associated with the physical calculations. A cytogenetic study program of the survivors was initiated in the late 1960s at the Atomic Bomb Casualty Commission (the ABCC, which was the predecessor of the current Radiation Effects Research Foundation or RERF). Unfortunately, however, although dicentrics are the best biomarker to use for biodosimetry, cells bearing these aberrations cannot continue to divide, and hence are negatively selected against, which results in a decrease in the frequency of dicentric-bearing lymphocytes with a half-time of several years [22]. Therefore, detecting reciprocal translocations (the counterpart of dicentrics) was the only practical choice for a marker to use in these experiments, but detecting these reciprocal translocations was much more difficult with the ordinary solid Giemsa staining method.

Among the cytogenetic studies conducted at RERF, results on the survivors exposed in utero were exceptional; namely, almost no effects of radiation were detected in blood lymphocytes when the survivors were examined at around 40 years of age [14]. These results were quite unexpected because fetuses were thought to be highly sensitive to radiation exposures judging from the OSCC study and other antecedent studies. Because the physically estimated doses depended on the subject's personal memories and thus were not free from various types of errors, the mothers of the survivors exposed in utero were also examined and it was shown that their blood lymphocytes did record radiation damage as would be expected. Pair-wise comparisons of mother-child data clearly demonstrated that lack of radiation effects was only seen in the offspring, and this excluded the possibility of errors in the physically estimated doses [14]. Although there appeared to be a slight, but statistically significant rise in the translocation dose response at low doses (around 3 cGy), that dose range is too low to use to confirm or negate the results with animal experiments, and hence this issue remains unresolved. In contrast, at higher doses, no detectable increase was seen. These results had no relationship to the developmental stage (trimester) of the embryo/fetuses at the time of their radiation exposures.

Animal Studies

In order to confirm that the observations made on the A-bomb survivors who were exposed in utero are valid in other mammals, mouse studies were conducted [23, 24••]. In the first series of the experiments, mouse fetuses at 15.5 days post conception (E15.5) were exposed to various doses of radiation and the frequency of chromosome aberrations was examined after birth when the animals reached 20 weeks of age. As was observed in the A-bomb survivors exposed in utero [14], the results did not show a significant increase of translocation

frequencies in blood lymphocytes, spleen cells, or bone marrow cells. Subsequent experiments in which neonates were exposed to radiation also did not show increased aberration frequencies (cytogenetic examinations were conducted when the animals reached 20 weeks old as in the experiments of fetal irradiation). When the age at the time of irradiation was further increased from 10 days old to 13 weeks old, the translocation frequencies observed in adults (20 weeks old) were quite low if the mice had been irradiated at 1 to 2 weeks of age, but the frequencies gradually increased following an increase in the age at exposure, and finally reached the same level as that seen in mice irradiated as adults if the irradiation took place at an age of 6 weeks or older.

It was suspected that apoptotic cell death might have contributed to the elimination of damaged cells. To study this, mouse fetuses bearing TP53 null alleles under homozygous conditions were irradiated, but the results remained the same [23]. Therefore, P53-dependent apoptosis does not seem to be the underlying cause for the lack of evidence showing radiation-induced damage in fetal lymphoid cells, although possibly other apoptotic pathways could be involved.

One interesting observation following irradiation in utero (both in humans and in mice) was that identical translocations could be observed in different cells (i.e., these were clonal descendants), even though the frequencies of the translocations were quite low (see reference [24••] for mice, and [25] for humans). This observation is quite contrary to what was found for post-natally exposed survivors: clonal aberrations were mostly found among people whose translocation frequencies were highly elevated (i.e., in high-dose survivors) [26, 27]. In such cases, one can easily expect that hematopoietic stem cells (HSCs) bearing radiation-induced unstable-type chromosome aberrations undergo subsequent mitotic-linked cell death, whereas surviving stem cells carrying stable-type aberrations (e.g., translocations, inversions) can expand clonally and eventually participate in the recovery from acute tissue damage. The finding that clonal aberrations were also seen following fetal exposures to radiation where the translocation frequencies were quite low indicated that while the majority of HSCs that had born radiation-induced chromosomal aberrations were somehow eliminated, a small number of stem cells could have survived, but were marked chromosomally with different translocations and could act sufficiently as functional stem cells able to sustain a lymphoid cell pool. These observations could help form a unique model to indicate when adult-type, long-term hematopoiesis starts to take place during the fetal life (this is difficult to study by using genetic manipulations of fetal HSCs; [28, 29]).

Other reports indicate that tissue stem cells could possess some type of mechanism (which most likely operates via apoptosis) to eliminate damaged cells. For example, the radiation dose necessary to kill 50% of exposed cells (the LD50) is about 150 mGy in immature oocytes of juvenile mice [30] and

10–50 mGy in intestinal crypt stem cells in adult mice [31]. Also, fetal brain cells become highly sensitive to the lethal effects of radiation at the time when large numbers of cell divisions take place [32, 33]. These LD50 values are very small when compared with typical LD50 values of 1 to 2 Gy for cultured mammalian cells in vitro (but cultured cells do not die via apoptosis, but during cell division).

Radiation Effects on Non-hematopoietic Fetal Stem Cells in Rodents

We next asked if the observed lack of clear evidence of radiation damage was restricted to hematopoietic cells (bone marrow cells or lymphocytes), or if evidence of radiation damage could be observed in cells of other solid tissues. For this purpose, we chose to examine mammary stem cells in rats. E17.5 rat fetuses were exposed to 2 Gy of gamma rays, and when the animals reached 6, 9, and 46 weeks of age, the mammary glands were removed and subjected to short-term tissue cultures for cytogenetic examinations. The results were completely different from those for HSCs: regardless of the age at the time of examination, the translocation frequencies were nearly the same as those found in the mothers or in rats irradiated as adults. Blood lymphocytes from the same animals did not show any evidence of radiation damage, as had been seen in mice [34••]. These results demonstrated that the lack of evidence of radiation effects could be a unique characteristic of fetal HSCs.

Mouse thyroid cells were then tested [12••]. In this study, fetuses were irradiated not only at E15.5 (during the fetal developmental stage), but also at an earlier time at E6.5 (as an embryo and before the start of the organogenesis period). When the animals reached 8 to 12 weeks of age, the thyroid glands were removed and were subjected to short-term tissue culture and cytogenetic examinations. The results showed that following irradiation at E15.5 (in the fetal stage), the translocation frequencies were nearly the same as those in the mothers, which was an observation similar to those obtained from rat mammary epithelial cells. However, in mice irradiated as embryos at E6.5, translocation frequencies determined as adults were quite low in both thyroid and lymphoid cells.

In summary, the radiation effects on a fetus differ not only among tissues (hemato-lymphoid cells vs. mammary or thyroid epithelial cells), but also depending on the developmental stage at the time of exposure (e.g., E6.5 vs. E15.5 in the mouse).

Differences Between Humans and Mice

Understanding species differences with respect to the time course of intrauterine development is an important issue because the total length of gestation can be quite different among

different mammals, e.g., about 20 days for mice and rats and about 9 months for humans. The difference is attributed primarily to the much longer post-embryonic, fetal stage in humans. With regard to hematopoiesis, embryonic blood formation (primary blood formation) takes place transiently in the yolk sac around E7 in the mouse and around E21 in humans. Subsequently, the secondary stage of blood formation (adult-type blood formation) takes place in the aorta-gonad-mesonephros (AGM) at around E10.5 in the mouse and around E40 in humans. Next, hematopoiesis takes place in the fetal liver (and spleen) where extensive stem cell proliferation occurs (at E11–16 in the mouse and around E70 in humans), followed by the cells moving into a final niche in the bone marrow where the HSCs become quiescent. This final move to the bone marrow niche starts before birth in humans but occurs mainly after birth in the mouse [35, 36].

Working Hypothesis

Our mouse data showed that irradiation of not only fetuses, but also of neonates, gave rise to only a very low yield in the translocation frequency which could persist until the animals became adults. Only after an irradiation at the age of 2 weeks or older did the translocation frequency start to persist [23]. Since it is reported that in the mouse, large-scale hematopoiesis in the bone marrow starts 3 to 4 weeks after birth [37], our observations indicate that when fetal HSCs which have not yet settled in a bone marrow niche were irradiated, the damage is somehow effectively eliminated. It seems that it is only after the cells have settled in their bone marrow niche that radiation-induced aberrations can start to become persistent. Preliminary data on A-bomb survivors who were exposed to radiation as infants (under one year of age) did not show radiation damage, which was the same result seen in survivors who were exposed in utero. In contrast, survivors who were exposed at ages of 5 years or older showed translocation yields similar to that seen in adults after exposures (Y. Kodama et al., manuscript in preparation). If we accept the idea that HSCs that bear chromosomal aberrations do not persist if they were irradiated prior to their settling in an appropriate niche, then two alternative hypotheses can be suggested to explain possible underlying mechanisms (Fig. 1).

Hypothesis 1 assumes that the repair of DNA damage does not take place effectively in fetal HSCs prior to their settlement in a bone marrow niche. This mechanism is probably the most cost effective, i.e., if the rejoining of DNA strand breaks does not take place, the cells would be arrested in the cell cycle and blocked from progressing to further cell divisions. Even if cells were released from a cell cycle arrest under these conditions, acentric fragments would be lost during subsequent cell divisions leading to genomic deficiencies or break-fusion cycles, which would ultimately lead to strong negative selection

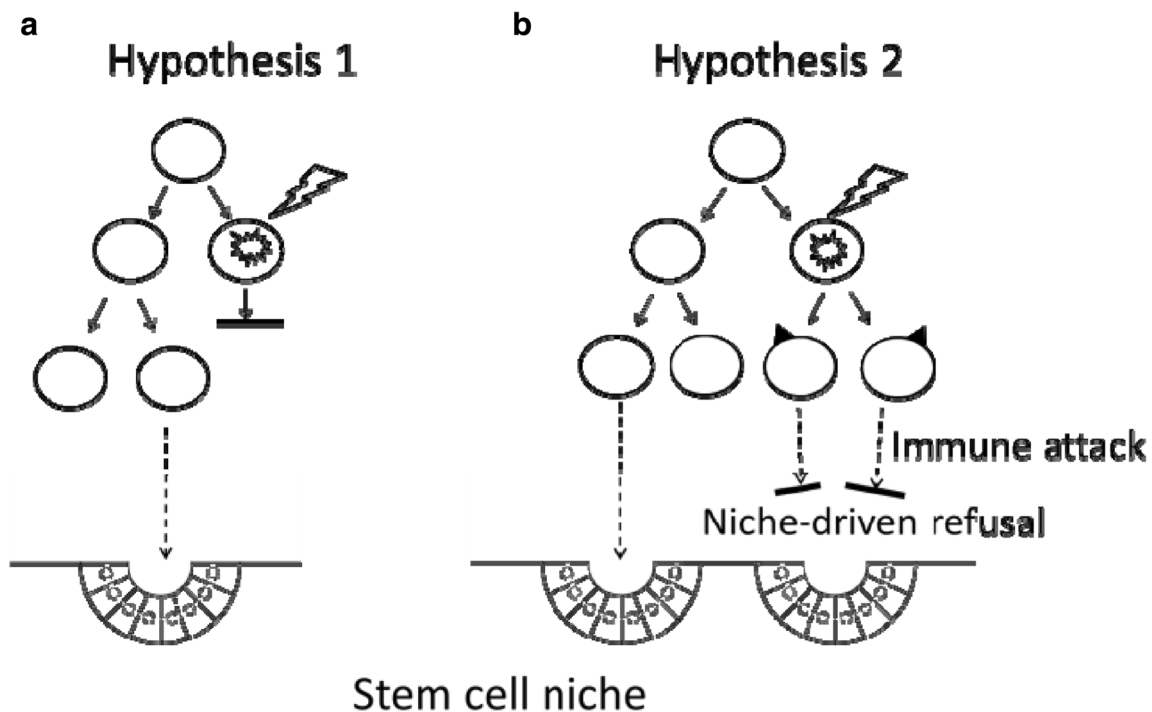


Fig. 1 Hypotheses to explain the lack of evidence of radiation damage in fetal hematopoietic stem cells (HSC). **a** Hypothesis 1 assumes that radiation-induced chromosome breaks are left unrepaired so that the damaged cells may be automatically subjected to negative selection. **b**

Hypothesis 2 assumes that HSCs can effectively repair DNA double-strand breaks, but such cells are somehow recognized and suppressed from entering the niche

against the damaged cells in the stem cell pool. Mis-repair of DNA breaks in stem cells (which leads to formation of exchange-type chromosomal aberrations) would probably take place only after the cells had entered their appropriate niche. Indeed, irradiation of early mouse embryos gave rise primarily to chromosome or chromatid breaks (deletions), and far fewer exchange-type aberrations [38, 39••], which indicates that low levels of DNA repair activity could be a common feature in early embryonic cells and early tissue stem cells.

Hypothesis 2 assumes that exchange-type aberrations can be formed in stem cells prior to their settling in their niche, but such aberration-bearing cells are subjected to a nearly complete negative selection when entering the bone marrow niche. The weakness of this hypothesis is that translocation-bearing cells would have no mechanical problems in pursuing continued cell divisions. This means that one has to assume that there is some type of unknown selective activity which is exerted from outside of the stem cells themselves, e.g., chromosomally damaged cells might express a surface signal indicating that “repair activity has occurred, so I must be deleted.” This might be possible if some molecules associated with DNA repair processes, for example, could be transferred to the cellular membrane or somehow affect the cell membrane, which could then permit recognition by the immune system. Alternatively, such a signal may be used by the bone marrow

niche to refuse HSCs that had experienced repair activity to settle into place. There is a report of a niche-driven negative selection process which is known to accept only non-cycling HSCs into the niche, but not cycling HSCs [37].

Nonetheless, a question still remains: it has been established that specific chromosomal translocations associated with childhood leukemia (mainly ALL) occur in pre-B cells during fetal life [16, 17]. Thus, it is of interest to ask why signals which lead to the elimination of translocation-bearing cells are not expressed in the pre-B cells. It might be because such pre-B cells have already settled into an appropriate niche when they began the differentiation process, and hence, tumor-causing translocations might not be able to express signals which could lead to a negative selection. Alternatively, molecular mechanisms involved in radiation-induced translocations might be different from spontaneous leukemia-specific ones. Another possibility is that the fusion proteins produced by leukemia-specific translocations can function as suppressors working against any negative selective forces in a manner similar to the anti-apoptotic function of BCL-2 in the genesis of lymphoma [40].

In either case, we think it would be possible to isolate long-term (LT) HSCs ($\text{Lin}^- \text{Sca1}^+ \text{c-kit}^+ \text{CD150}^+ \text{CD48}^-$) from the livers of newborn mice that were irradiated as fetuses, and examine their chromosomes. If hypothesis 1 is correct, long-term (LT)-HSCs bearing chromosomal aberrations would

disappear within a few days after the irradiation of a fetus, while if hypothesis 2 were correct, translocation-bearing fetal LT-HSCs would persist even after birth.

Future Perspectives

Our ultimate goal is to develop a mouse model of human childhood ALL, and examine whether fetal exposures to radiation can lead to an increase in the frequency of early-onset leukemia. However, past attempts by other research groups to establish such mouse models were not successful [41]. If radiation exposures of such mice show evidence for radiation damage in pre-B cells, it would appear that abdominal X-ray exposures could have contributed to the development of childhood leukemia in humans. On the other hand, if fetal pre-B cells were found to be incapable of recording persistent radiation damage like fetal HSCs, the epidemiologic results from the OSCC study and other similar studies might actually indicate that X-ray exposures may not be the true culprit responsible for leading to an increased risk of developing childhood leukemia. With regard to this, it is known that a heavy birth weight in newborns is associated with elevated risks for developing childhood leukemia (e.g., [42, 43]). This also seems to apply to some extent to other childhood cancers (e.g., [44]). Therefore, one hypothetical scenario is that pregnant women who bore large fetuses could have been subjected to a higher probability of having been exposed to radiation during an examination of the pelvis and fetus to determine if fetal head sizes were not too large for vaginal deliveries, or if cesarean deliveries should be considered (i.e., to avoid dystocia due to cephalopelvic disproportion or CPD). There is one report which examined the birth weights in estimating the risk of abdominal X-ray exposures, but no effect of birth weight was seen on the risks of childhood cancer following prenatal X-ray exposures [45, 46]. It is hoped that additional information such as the height of the mothers, which could be another reason to take the X-ray photographs to avoid CPD, can be compiled so that this issue may be pursued in further detail.

One can argue that the risks following fetal exposures to radiation have little or nothing to do with modern medicine since X-ray exposures have been largely replaced by non-radiation generating probes such as ultrasonography. However, this continues to be an important area of research because past case-control data indicate that a single exposure to 1 cGy could lead to a measurable detrimental effect in humans [8, 10]. Furthermore, the increased risks were found for all childhood solid cancers in the case-control studies, which is not the case in A-bomb survivors exposed in childhood (Table 1). The difference could illuminate important aspects of etiology. It is hoped that information provided from a biologist's viewpoint can answer questions posed by epidemiologists.

Conclusion

It still remains unclear whether or not prenatal exposure to radiation caused the observed increased risk for childhood leukemia and solid cancers later in their lives.

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Compliance with Ethical Standards

Conflict of Interest Kanya Hamasaki and Nori Nakamura declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Disclaimer The views of the authors do not necessarily reflect those of the two governments.

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