The Effects of Iodine Blocking Following Nuclear Accidents on Thyroid Cancer, Hypothyroidism and Benign Thyroid Nodules

Part of: *WHO guidelines for iodine thyroid blocking in a nuclear or radiological accident*

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HZ, MP and SD developed the protocol; HZ, LC and SL provided comments on the first and all subsequent versions. LC conducted the literature searches. MP and SD reviewed and selected abstracts and reports. HZ and MP did the research synthesis and evaluated the quality of literature. HZ and SL acted as third reviewers. HZ and MP wrote the final report.

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Abstract

Background: One of the most efficient radiation protection methods to reduce the risk of adverse health outcomes in case of accidental radioactive iodine release is the administration of potassium iodine (KI). Although KI administration is recommended by WHO's Guidelines for Iodine Prophylaxis following Nuclear Accidents and is also widely implemented in most national guidelines, the scientific evidence for the guidelines lacks as the guidelines are mostly based on expert opinions and recommendations. Therefore, this study provides evidence by systematically reviewing the effects of KI administration in case of accidental radioactive iodine release on thyroid cancer, hypothyroidism and benign thyroid nodules.

Objectives: To assess the effects of KI administration on thyroid cancer, hypothyroidism, and benign thyroid nodules in a population exposed to radioiodine release.

Methods: We applied standard systematic review methodology for the identification of eligible studies, data extraction, assessment of risk of biases, heterogeneity, and data synthesis. The electronic database search was conducted in MEDLINE (via PubMed) and EMBASE, and covered three search blocks with terms related to the health condition, intervention, and occurrence/location. We had no date or language restrictions, but restrictions to humans only. We included studies comparing the effects of KI administration on thyroid cancer, hypothyroidism and benign thyroid nodules in a population exposed to radioactive iodine release. The quality of the studies was graded. It was not possible to conduct a meta-analysis.

Results: We found one cross sectional study, one analytic cohort study and two case-control studies relating to our question. Numbers of participants ranged from 886 to 12,514. Two studies were in children and two other studies were in children and adults. KI administration after a nuclear accident resulted in a reduction of the risk of thyroid cancer in children. None of the studies investigated the effects of KI administration in case of nuclear accident on hypothyroidism and benign thyroid nodules.

Authors' conclusions: The results suggest that KI intake following a nuclear accident might be an effective means of reducing the risk of thyroid cancer in children. No conclusions can be drawn about the effectiveness of KI intake with respect to the prevention of hypothyroidism and benign thyroid nodules.

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Keywords: Stable oral iodine, potassium iodine, Chernobyl, health outcomes, I-131, reactor accident

Zusammenfassung

Hintergrund: Die Verabreichung von Kaliumjodid gehört zu den effizientesten Strahlenschutzmaßnahmen bei der Reduktion gesundheitlicher Folgeschäden im Falle einer unvorhergesehenen Freisetzung radioaktiver Stoffe. Obwohl die Gabe von Kaliumjodid in den Richtlinien der WHO zur „Jodprophylaxe in Folge eines nuklearen Unfalls“ empfohlen wird und auch in den nationalen Richtlinien weitgehend eingebettet ist, fehlt jegliche wissenschaftliche Evidenz für die Richtlinien, da diese hauptsächlich auf Expertenmeinungen und Empfehlungen basieren. Um die Evidenzlage zu stärken, untersucht diese Studie systematisch die Effekte einer Kaliumjodideinnahme auf Schilddrüsenkrebs, Hypothyreose und gutartige Schilddrüsenknoten im Falle eines nuklearen Unfalls.

Ziele: Ziele sind die Evaluierung der Auswirkungen einer Kaliumjodideinnahme auf Schilddrüsenkrebs, Hypothyreose und gutartige Schilddrüsenknoten bei Menschen, die der Freisetzung von radioaktiven Stoffen ausgesetzt sind.

Methodik: Wir verwendeten standardisierte Methoden zur Durchführung von systematischen Übersichtsarbeiten für die Identifizierung geeigneter Studien, für die Datenextraktion, für die Bewertung von Verzerrungsrisiken, für die Identifizierung von Heterogenität und für die Datensynthese. Die elektronische Datenbanksuche wurde in MEDLINE (über PubMed) und EMBASE durchgeführt. Die Suche beinhaltete drei Suchblöcke mit Terminologien zur Gesundheitsbedingung, der Intervention sowie dem Auftreten/der (geographischen) Lage des nuklearen Unfalls. Unsere Suche hatte keine Restriktionen bezüglich Publikationsdatum und Sprache, allerdings betrachteten wir nur Studien in menschlichen Populationen. Wir inkludierten Studien, die die Effekte der Kaliumjodideinnahme auf das Risiko von Schilddrüsenkrebs, Hypothyreose und gutartige Schilddrüsenknoten bei Populationen, die radioaktiver Strahlung in Folge eines nuklearen Reaktorunfalls ausgesetzt waren, untersuchten. Die Qualität der Studien wurde bewertet. Wir konnten keine Metaanalyse durchführen.

Ergebnisse: Wir haben eine Querschnittsstudie, eine analytische Kohortenstudie und zwei Fall-Kontroll Studien, die sich auf unsere Forschungsfrage beziehen, gefunden. Die Teilnehmeranzahl liegt im Bereich von 886 bis 12.514. Zwei Studien inkludierten nur Kinder und zwei weitere Studien hatten sowohl Kinder als auch Erwachsene inkludiert. Die Einnahme von Kaliumjodid in Folge eines nuklearen Unfalls resultierte in einer Reduktion des Schilddrüsenkrebsrisikos bei Kindern. Keine der Studien untersuchte die Effekte der Einnahme von Kaliumjodid in Folge eines nuklearen Unfalls auf Hypothyreose und gutartige Schilddrüsenknoten.

Schlussfolgerung der Autoren: Die Ergebnisse deuten darauf hin, dass die Einnahme von Kaliumjodid in Folge eines nuklearen Unfalls eine effiziente Methode zur Reduktion des Schilddrüsenkrebsrisikos bei Kindern ist. Über die Effizienz einer Kaliumjodideinnahme zur Prävention von Hypothyreose und gutartigen Schilddrüsenknoten kann keine Aussage getroffen werden.

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Schlüsselwörter: Kaliumjodid, Tschernobyl, I-131, gesundheitliche Folgen, Reaktorunfall

Background

Description of the condition

Radioactive isotopes of iodine (I-131) are generated in large amounts as a by-product of uranium fission, which is primarily used in nuclear reactors for energy production. In the event of a nuclear reactor accident and when radioactive material is released to the atmosphere, I-131 may be incorporated into the human body through inhalation or ingestion of contaminated food and milk [1]. When inhaled, about 10-30% of the radioactive iodine will primarily accumulate in the thyroid gland while the remaining amount will be discharged from the body with the urine [2]. As part of I-131's decay process, beta-radiation is emitted and affects the thyroid and its surrounding tissue, and may lead to adverse health outcomes such as thyroid dysfunctions and thyroid cancer.

From the Life Span study, there is evidence for the development of benign and malignant thyroid nodules as a result of external exposure to ionizing radiation among the atomic bomb survivors [e.g., 3]. Following the Chernobyl reactor accident, which involved a large release of I-131 into the environment, significantly increased numbers of thyroid cancer and thyroid dysfunction such as hypothyroidism were observed in individuals from highly contaminated regions in Ukraine and Belarus [4-6]. In addition, children and adolescents have been found at higher risk for developing thyroid diseases compared to adults. This is due to their smaller thyroid gland, its development during childhood and adolescence which leads to a 5-10 fold increase of committed thyroid dose, higher uptake of radioiodine, and higher sensitivity to radioiodine release of the organs, tissues and cells [7-9]. Further, it is suggested that radiation exposure during the prenatal phase is associated with an increased risk for thyroid cancer [10], and I-131 transmission from mother to infant during breastfeeding has been investigated as an additional risk factor for infants to develop thyroid cancer in later stages in life [11, 12]. In contrast, radiation-induced thyroid cancer risk for adults is thought to be very low and may be close to zero [13].

Description of the intervention and how it might work

The oral administration of potassium iodine (KI) is assumed to be the most effective and preventive radiation protection measure to reduce the risk of adverse health outcomes for the exposed population in the event of an accidental release of radioactive iodine [14, 15]. KI essentially saturates the iodide transport mechanism of the thyroid by inhibiting the intrathyroid organification of iodide (acute Wolff-Chaikoff effect), by dilution and by promoting excretion and thus, reducing the amount of committed dose to the thyroid gland, its surrounding tissue and the body [16-18].

KI administration depends on the predicted exposure levels to the thyroid of the defined population groups (i.e. intervention/action levels). KI doses further vary to account for the respective risks of vulnerable population groups (newborn, children and adolescents, and pregnant and lactating women). The effective blocking of the thyroid is achieved with a dose of 130 to 170mg of potassium iodine. Fractions of these quantities are to be used in specific population groups (1 in adults, adolescents in addition to pregnant and lactating women, if necessary; 1/2 in children; 1/4 in infants; 1/8 in newborn) [19, 20]. Although KI

administration blocks the thyroid gland, it does not provide complete protection from accumulating radioactive iodine. A single dose of KI approximately blocks the thyroid between 24 and 36 hours but the blocking capacity decreases with increased time after administration [19, 21]. In the event of continuous release of I-131, repeated administration may be required to ensure prolonged protection of the general population as the protective effect of one KI dose decreases with time.

The Polish government initiated KI administration in the Polish general population, in particular in children and adolescents, in late April and early May 1986 as a consequence of the reactor accident in Chernobyl and the subsequent discharge of radioactive iodine to the environment. Assessing the efficacy of KI administration, Nauman and Wolff [22] estimated a reduction in committed thyroid dose between 40% and 62% for those children who were administered KI one to four days after the start of exposure. With regard to the timing of the intervention, a simulation study demonstrated higher protective KI efficacy when its administration is carried out in early exposure stages (78.9 vs. 39.1% with KI given within 2h or at 8h after uptake of radioactive iodine, respectively) [15]. It is notable that in Poland as a result of the immediate thyroid blocking measures implemented within the first 4 days after the start of the exposure it was achieved that about 90% of the children under the age of 16 showed thyroid dose commitments below the predicted mean maximal burden (<50mSv) in this risk group [22].

A recent systematic review further examined the adverse side effects of KI administration to block the thyroid [23]. The evidence gathered from the systematic review suggested that even the administration of high doses of KI did not result in serious adverse health outcomes in the exposed population groups. Severe reactions of clinical significance were rare and in particular observed in individuals with pre-existing thyroid disorders and iodine sensitivity. There was little data available on age differences. The review results however suggested that newborns and the elderly may experience more adverse side effects after KI administration compared to other age groups [23]. Overall, the evidence-base was relatively weak because with the exception of the Polish study by Nauman and Wolff [22] most studies on the effects of KI were primarily set in the clinical context and addressed exposure reduction as part of therapy procedures.

Why it is important to do this review

Iodine thyroid blocking using potassium iodine (KI) is regarded as the most effective radiation protection measure in the event of an accidental release of radioactive iodine to reduce the risk of adverse health outcomes for exposed populations. KI administration is endorsed by WHO's Guidelines for Iodine Prophylaxis following Nuclear Accidents and is also widely implemented in most national guidelines. To date, the current guidelines are primarily based on expert knowledge and opinion while the scientific base was not established and reviewed systematically.

As part of the update of the existing WHO guideline from 1999 [20], present WHO regulations for guidelines development require a systematic review of the scientific evidence in order to inform the updating process [24]. Thus, the present project aims to provide an up-to-date review on the efficacy of KI administration to reduce adverse health outcomes such as

thyroid dysfunctions and thyroid cancer for the general population in the event of an accidental release of radioactive iodine to the environment.

Objectives

We aim to assess the effects of KI administration on thyroid cancer, hypothyroidism, and benign thyroid nodules in a population exposed to radioiodine release.

In particular, it is necessary to assess whether specific population groups (e.g. children and adolescents between 0-18 years of age, pregnant or lactating women) are differentially affected by KI administration, and to identify appropriate timing, and in circumstances of repeated/continuous exposure, whether repeated KI administration may be warranted to reduce the accumulation of I-131 in the thyroid gland in the exposed population as compared to intervention.

The study's objective is based on the following PICO:

In a population exposed to radioiodine release (P), does the administration of KI for prophylaxis (I) against no administration (C) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)?

The following sub-PICOs are necessary to cover the main question fully:

In a population exposed to a single radioiodine release (P), does the timing of the administration of KI (prior, shortly after (I) or later than two hours (C)) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)

In specific subgroups of a population exposed to a continuous or repeated radioiodine release (P), does a repeated administration of KI (I) against a single administration (C) affect the risk of developing thyroid cancer, hypothyroidism, or benign thyroid nodules (O)?

Methods

Criteria for considering studies for this review

Types of studies

The review covers a broad spectrum of research questions that are not necessarily assessed in randomized clinical trials (RCTs). Thus, non-randomized studies were included in the review. More specifically, the following experimental and observational study types were covered:

- RCTs
- Quasi-RCTs
- Controlled before-after studies
- Time-series
- Cohort studies
- Case-control studies
- Surveys, e.g. pharmacoepidemological studies

Types of participants

Participants included in studies either are the general population and workers. No further specification is feasible. The literature search was limited to evidence from studies in humans.

Types of interventions

The interventions evaluated arise from the objectives as outlined above.

The following interventions were considered:

- Stable oral iodine/potassium iodine administration in the general population exposed to external ionizing radiation or radioactive iodine in the environment.

Types of outcome measures

The review included studies that report the following outcome measures

- Prevalence and incidence of radiation-induced thyroid cancer
- Prevalence and incidence of radiation-induced hypothyroidism
- Prevalence and incidence of radiation-induced benign thyroid nodules
- Mortality from radiation induced thyroid cancer (hypothyroidism and benign thyroid nodules are not considered to be associated with mortality)

Search methods for identification of studies

Electronic searches

After consulting Russian and Japanese experts on radiation for the inclusion of potentially relevant databases from other countries, we have decided in agreement with the international experts to search the following academic databases:

- MEDLINE (1946 to present)
- Excerpta Medica database (EMBASE) (1947 to present)

We developed detailed, database-specific searches using a broad set of relevant keywords and terms. We applied the search strategy with additional keywords for possible comparators and we did not use filters for study types to improve the results of the literature search with respect to the total number of relevant studies.

Databases as listed above were searched until 16 June 2015.

For details on the MEDLINE and EMBASE search strategies, see Appendix 1 and 2, respectively.

Searching other resources

All relevant records for additional relevant studies were searched by hand.

Advisory Group

We have established a review advisory group of experts in the field of thyroid cancer, iodine thyroid blocking and systematic reviews to further comment and provide advice and suggestions to improve the manuscript in protocol- and review-stage.

In protocol-stage, Christoph Reiners, Rita Schneider (UK Würzburg, Germany), Elie Akl (AUB, Beirut, Lebanon), Zhanat Carr, and Susan Norris (both WHO) provided feedback on the research questions. Tomas Allen (WHO) provided feedback on the search strategy and the selected databases. Vladimir Saenko (Nagasaki University, Japan) supported the literature search.

Data collection and analysis

Selection of studies

A research librarian assisted the database search for relevant studies (LC). First, studies' titles and abstracts, if feasible, as identified by the search were reviewed by two authors independently (SD, MP). Second, both reviewers compared their list of relevant studies and in case of any disagreement the opinion of a third author was decisive (HZ). Additionally, a third author screened the list of relevant studies (HZ). Third, full texts of potentially relevant studies were retrieved or obtained. Fourth, the full texts were screened by the reviewers independently (SD, MP). Fifth, each reviewer created a list with studies that were considered

to fulfill the inclusion criteria. Sixth, the reviewers compared their list with each other and in case of any disagreement the opinion of a third author was decisive.

Based on these six steps, studies were included for the review. A flowchart based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) was developed to visualize the selection of included studies (see Figure 1). Moreover, we provide a table with statements on excluded studies (see Appendix 3).

Data extraction and management

Data extraction was performed by two authors independently (SD, MP). In case of any disagreement, the opinion of a third author was decisive (HZ). We used a modified data extraction and assessment template from the Cochrane Public Health Group (CPHG). Previous to the major data extraction process, the authors piloted the data extraction form to ensure a standardized extraction. We extracted general information (publication type, country of study, funding source of study, potential conflict of interest from funding), study eligibility (type of study, participants, type of intervention, duration of intervention and type of outcome measures), study details (study intention, methods, results, intervention group, outcomes), and other relevant information.

We have planned that one author assembles and inserts data into RevMan 5.3, if feasible.

Assessment of risk of bias in included studies

The risk of bias of every included study was evaluated by two authors independently (SD, MP). In case of any disagreement, the opinion of a third author was decisive (SL). Based on the template provided from the CPHG, the risk of bias was assessed using the criteria for judging risk of bias in Cochrane's 'Risk of bias' assessment tool and the Cochrane Effective Practice and Organisation of Care (EPOC) Group's guidance for interrupted time series (ITS) tool. Cochrane's 'Risk of bias' assessment tool and the EPOC risk of bias tool for ITS examine the following biases: selection, performance, detection, attrition, reporting, and others. The EPOC risk of bias tool for ITS examines three further risks of bias: "Was the intervention independent of other changes?", "Was the shape of the intervention effect pre-specified?" and "Was the intervention unlikely to affect data collection?"

Assessment of the risk of bias in cohort studies followed the best practice recommendation to assess the specific features of cohort studies and the extent to which these may introduce bias [22, 23]. We assessed the risk of bias in the following features: sampling strategy; response rates; sample representativeness; attrition; participant allocation; exposure assessment; outcome assessment; reporting and control of key confounders and control of reverse causation.

To judge the risk of bias according to Cochrane's 'Risk of bias' assessment tool, the following three categories were used: no" (risk of bias is low), "yes" (risk of bias is high), and "unclear" (information lacks or uncertainty about the risk of bias) [24].

To judge the risk of bias according to the Quality Assessment Tool for Quantitative Studies, the following three categories were used: “strong”, “moderate”, and “weak” [25].

Unit of analysis issues

We planned to consider the level at which randomization occurred, e.g. cluster-randomized trials, cross-over trials, and multiple observations (repeated observations on subjects, recurring events, multiple body parts, and multiple intervention groups) for the same outcome [24].

In the included studies, randomization did not occur.

Dealing with missing data

We planned to contact study authors if relevant data is missing. Data “not missing at random” due to publication bias, systematic loss to follow-up or systematic exclusion of individuals from studies were planned to be identified and requested from study authors.
In this review, relevant data were not considered to be missing.

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, we planned not to perform meta-analytic pooling.

We planned to detect heterogeneity through visual inspection of the forest plots and by using a standard Chi^2 test with a significance level of $P < 0.1$ [24]. We planned to apply the I^2 statistic to quantify inconsistency across studies and to assess the impact of heterogeneity on the meta-analysis [24]. Potential reasons for heterogeneity were planned to be examined by conducting subgroup analyses. However, as indicated below, the low number of studies included did not enable us to statistically investigate issues related to heterogeneity.

Assessment of reporting bias

Reporting biases, including publication bias, time lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias, and outcome reporting bias, occur when the dissemination of research results depends on their magnitude and direction [24]. Study quality and risk of bias of randomized controlled trials were assessed with the Cochrane risk of bias tool [24]. Study quality and risk of bias of non-randomized quantitative studies were assessed with Quality Assessment Tool for Quantitative Studies [25]. We planned to apply funnel plots for visual assessment for study effects resulting from reporting biases if feasible. When testing asymmetry in funnel plots (small study effects) we planned to investigate whether the size of the relation between a measure of study size and the estimated intervention effect is larger than it is supposed to be [24]. We planned to use RevMan 5.3 for the graphical representation of the funnel plots.

Data synthesis

We planned to perform meta-analyses by applying RevMan 5.3 for study results with clinical, methodological, and statistical homogeneity, if feasible. For dichotomous outcomes, we planned to apply the Maentel-Haenszel method, and for continuous outcomes, we planned to apply the inverse variance method. For all analyses, the random-effects method was planned to be applied.

As we did not identify enough papers with sufficient homogeneity, we decided against doing a meta-analysis.

However, the study results with insufficient homogeneity were presented in a narrative synthesis. We provided a 'GRADE evidence profile' table [24] (Appendix 4). This table includes information on the outcomes, the study design, the relative and absolute effect, the number of patients, the number of studies included, the quality assessment and the overall quality of evidence (GRADE).

If there are data available for meta-analysis in the future, we will proceed as follows: Data synthesis aims to report changes in outcome measures from baseline to the post-intervention phase. Dichotomous data will be expressed as odds ratios (ORs), risk ratios (RRs) or risk differences (RDs). In accordance with the recommendations from the Cochrane Public Health Group, RRs will be the preferred reported data type. If RRs are not presented in the study, but data to calculate the RRs are provided, we will calculate them. If data to calculate the RRs are not provided, we will contact the corresponding author of the study for the RRs or the data to calculate the RRs by email or phone. If we cannot provide RRs, we will use the data provided in the study to report the treatment effect.

Continuous data will be expressed as standardized mean differences (MDs). Shorter ordinal data will be translated into dichotomous data (expressed as ORs, RRs or RDs) and longer ordinal data will be treated as continuous data (expressed as the standardized MDs). Count data and Poisson data will be expressed as rate ratios. Time-to-event data (survival data) will be translated into dichotomous data when appropriate or into hazard ratios (HRs).

Subgroup analysis and investigation of heterogeneity

We intended to investigate the following subgroups for primary outcomes:

- Children and adolescents (0-18 years) versus adults
- Males versus females
- Pregnant and lactating women versus other women
- Dosage of intervention (e.g. low or high)
- Timing of intervention (e.g. before, shortly after, or long after exposure)
- Timing of exposure (e.g. one time, two or more times, continuously)
- Magnitude of exposure (e.g. strong or weak)
- Repetition of intervention (e.g. after single, several or continuous exposures)

However, subgroup analyses and investigation of heterogeneity were not feasible given the small number of relevant papers and the notable lack of specific information on subgroups.

Sensitivity analysis

Sensitivity analyses were intended to be performed to determine the robustness of our results. To assess the impact of risk of bias we planned to conduct meta-analyses:

- with studies considered as ‘low risk of bias’ and then compare results to those of studies considered as ‘high risk of bias’
- with ‘large studies’ and then compare the results to those of ‘small studies’
- with published studies and then compare results to those of unpublished studies

However, sensitivity analyses were not feasible.

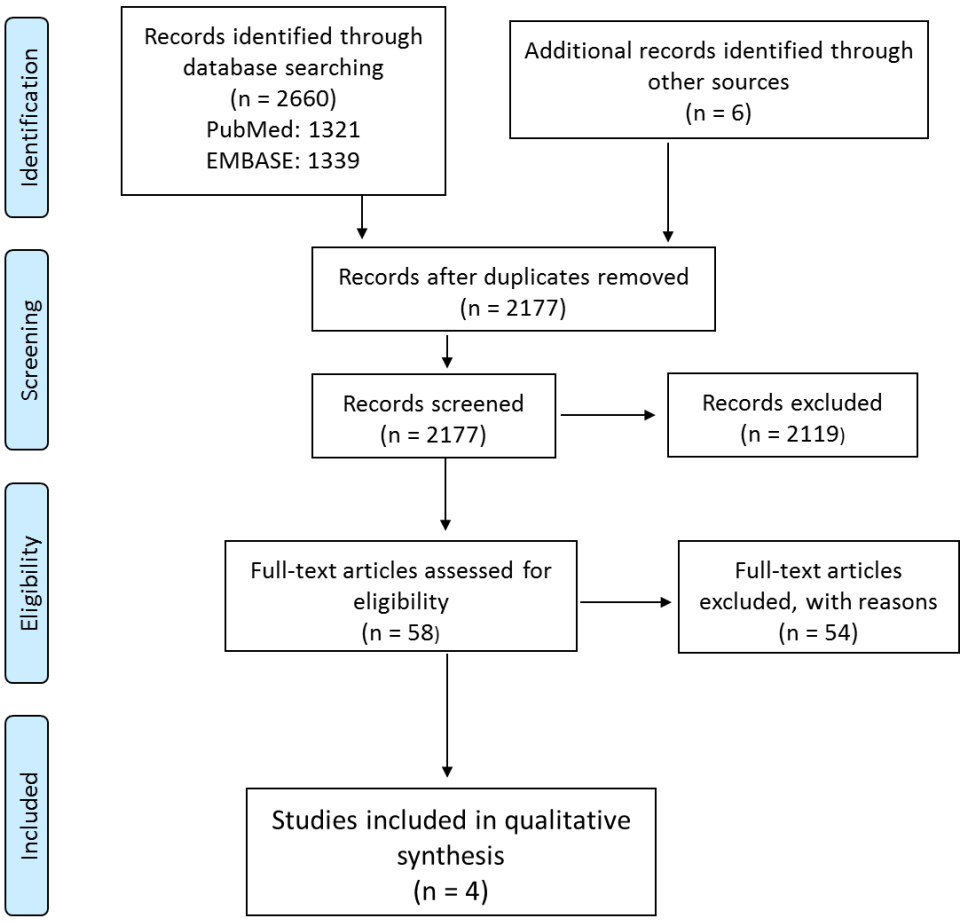
Results

Description of studies

Results of the search

We initially identified 2,260 records. From these, we recognized 58 potentially relevant publications for full text assessment for eligibility. The other records were excluded on the basis of their titles, abstracts, or both because they did not fit our research questions or did not meet the inclusion criteria. After screening the full texts and excluding eight clinical experimental studies, four simulation studies, five dosimetry studies, eleven papers categorized as note, editorial, dossier or policy review, eight overview papers on KI administration and distribution, two papers with missing outcomes, two papers with missing interventions, and 14 Polish papers screened by a native speaker that did not meet the inclusion criteria, four studies fulfilled the inclusion criteria. For details, see Figure 1 amended PRISMA flow diagram of study selection.

Figure I. Study flow diagram



Included studies

Details of the characteristics of included studies are shown in Appendix 5.

Study design

Of the four included studies, two studies are case-control studies [9, 26], one study is an analytic cohort [27], and one study is a cross-sectional study [28]. Countries of study were Ukraine [27], Belarus and Russian Federation [9], and Poland [26, 28].

Participants

Numbers of participants ranged from 886 to 12,514. The case-control studies had 1,576 and 886 participants respectively [9, 26]. In the larger case-control study, participants were younger than 15 years and in the smaller one, participants were between 0 and 85+ years. In the analytic cohort study, 12,514 participants younger than 18 years were involved. The cross-sectional study had 1,457 participants in the age of 6 to 55 years [28].

Interventions

In all studies, some subjects received KI. Although one study mentions that some participants repeated KI intake and some participants took KI during the following five days after the nuclear accidents whereas others received KI later, the differences in the health effects according to dosage and timing were not investigated [28].

Outcomes

None of the studies assessed hypothyroidism and benign thyroid nodules. Measured outcomes were Antithyroid antibodies (TA) including Anti-Human Thyroid Membrane Antibodies (ATMA) and Anti-Thyreoglobulin Antibodies (TGAb) [28], and thyroid cancer [9, 26, 27]. TA were measured with the ELISA method using Plastomed reagent kits. Thyroid cancer was generally defined as histologically confirmed cancer that was diagnosed after clinical and laboratory findings during screening examinations.

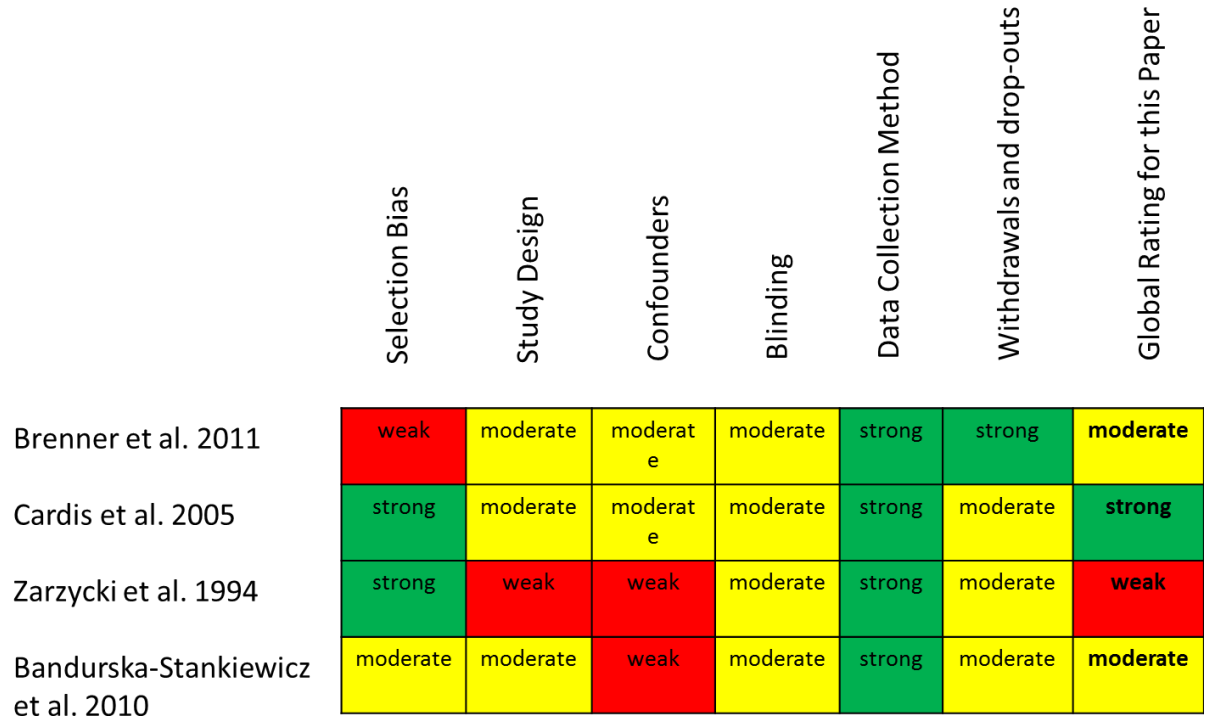
Excluded studies

Of the 58 studies, 54 were excluded upon further scrutiny. Reasons for exclusion are given in a summary of the characteristics of excluded studies, for details see Appendix 3.

Risk of bias in included studies

We have used GRADE according to Cochrane Guidelines for randomized controlled trials. However, as our study does not include RCT's, the study quality and risk of bias of non-randomized quantitative studies were additionally assessed with the Quality Assessment Tool for Quantitative Studies. The assessment of the methodological quality of the studies included is based on the Effective Public Health Practice Project (EPHPP) Guidelines, resulting in 'strong, moderate or weak' methodological quality. The methodological quality summary based on the EPHPP quality assessment tool is summarized in Figure 2.

Figure II. Methodological quality summary based on the Effective Public Health Practice Project Guidelines



Allocation

None of the studies was described as randomized or mentioned allocation concealment.

Blinding

None of the studies mentioned blinding of participants or blinding of outcome. It is unknown whether the outcome assessors were aware of the intervention or exposure status of participants and whether the study participants were aware of the research question.

Incomplete outcome data

Withdrawals and losses to follow-up were described only by one study [27]. None of the studies mentioned an intention-to-treat analysis.

Selective reporting

Selective reporting is not likely to have occurred as studies reported both significant and insignificant results.

Other potential sources of bias

Levels of KI administration and levels of exposure to radioactive iodine

In all studies, timing, exact dosage of KI administration (quantity and repetition) and levels of exposure to radioactive iodine are not clear. Therefore, the results might be biased by timing and dosage of KI administration and by levels of radioactive iodine exposure. On the other hand, given the absence of systematic procedures and pre-assessments in the situation where KI administration occurred, this bias can be considered as of limited relevance.

Effects of interventions

The effects of KI administration on ATMA, TGAb [28], and thyroid cancer [9, 26, 27] are shown in Appendix 4.

Anti-Human Thyroid Membrane Antibodies and Anti-Thyreoglobulin Antibodies

Zarzycki et al. [28] measured ATMA and TGAb. In the descriptive analysis they did not find significant differences between adult participants who took KI and the control group. Prevalence rates for ATMA were 13% in the KI group and 14% in the control group. Prevalence rates for TGAb were 10% in the KI group and 13% in the control group. The study population was too low to compare the effects of KI on ATMA and TGAb in children. In general, the study population was too small to run multivariate analyses.

Thyroid cancer

Three of four studies measured thyroid cancer [9, 26, 27]. Bandurska-Stankiewicz et al. [26] did not find significant differences between participants who took KI and the control group. Of the patients with thyroid cancer, 31% took KI. In the control group, 34% took KI, resulting in an OR of 0.87 (95% CI 0.65 to 1.18) for thyroid cancer after KI intake. Brenner et al. [27] investigated effect modification of the excess relative risk (ERR) of incident thyroid cancer per gray of exposure according to KI. The effect modification was insignificant (p=0.56), with an ERR Gy^{-1} of 2.11 (95% CI 0.36-9.28) for no KI administration and an ERR $Gy^{-1}$of 1.03 (95% CI <0.08-9.84) for KI administration. Based on data given, we calculated the relative risk of thyroid cancer after KI intake, based on person years, resulting in an OR of 0.68 (95% CI 0.36 to 1.28). Cardis et al. [9] reported a statistically significant threefold reduction (OR 0.31, 95% 0.1-0.9) in the risk of thyroid cancer at 1 Gy in the group who took KI as compared to the control group. This reduction was independent of soil iodide content in the respective area of residence.

Subgroup analyses

Not performed due to lack of data.

Sensitivity analysis

Not performed due to lack of data.

Discussion

Summary of main results

Expectedly, we did not find a randomized controlled trial relating to our study question. We included two case-control studies, an analytic cohort and one cross-sectional study. In total, the studies included did not assess many of the outcomes we considered important previously. Thus, we cannot report on the effect of KI in case of nuclear accident on two relevant outcomes, i.e. hypothyroidism and benign thyroid nodules. The studies identified relevant did not allow extracting information on subgroups. We cannot establish a dose-response relationship between KI intake and health outcomes as the studies did not assess different quantities and repeating intakes of KI. Two studies reported insignificant results on the relationship between prophylactic iodine and thyroid cancer. However, these studies show a tendency of decreased risks of developing thyroid cancer if KI was administered. This tendency was supported by a significant result from one study in children on considerably reduced risks of thyroid cancer after KI intake.

Overall completeness and applicability of evidence

The overall evidence base for the effect of KI administration after exposure to radioiodine release is rather incomplete, with the majority of studies investigating the association between KI intake and the risk of thyroid cancer.

The review included studies from different countries and regions. It becomes apparent that comparability of results across studies is difficult due to diverse magnitudes of exposure in the different geographical regions which were not always controlled for. However, the limited evidence available supports the suggestion that administration of KI is efficient for reducing the risk of adverse health outcomes after accidental release of radioiodine.

The studies included into the review focused on children, adults or both. Given the notion that children may be the most vulnerable population due to decreased absorption of radioiodine, considerable effects of KI intake on the risk of developing thyroid cancer in children younger than 15 years were reported from a study included in the review [9]. However, the results of our search imply that further studies need to assess whether effects differ between males and females and between pregnant and lactating women as compared to other women. The effect of dosage and timing of intervention and the magnitude and the timing of exposure need to be considered to receive a more accurate picture on the effects of KI on health outcomes after accidental release of radioiodine.

Quality of the evidence

The evidence base for outcomes was of very low to low quality. Key methodological limitations were control for confounding and the study design. Limitations in the study design and execution, as well as imprecision were major weaknesses for the outcomes. We currently lack requested author information from one case-control study to calculate the overall OR for thyroid cancer for this specific study design.

Potential biases in the review process

We have performed an extensive literature research. However, there could be relevant grey literature and unpublished studies that we did not find during the search process, and therefore, not consider in our review. We did, however, contact experts with specific overview over the publication landscape in Russian language as well as in Japanese to help us identify potential data sources or regional data bases of relevance for our study question. However, no additional relevant information was obtained.

We have studies from different geographical regions. Nevertheless, our results might not apply to all countries and settings similarly.

Significant results on decreased risks of thyroid cancer after KI intake following release of radioiodine are based on data in children. Therefore, application of our results to the general population needs to be done with caution.

Within and across studies, the timing and the quantity of KI intake was not specified, and therefore, the results might be biased in unknown ways.

Agreements and disagreements with other studies or reviews

This is the first systematic review on the effect of KI intake after a nuclear accident on thyroid cancer, hypothyroidism and benign thyroid nodules. Therefore, we cannot compare our results to other systematic reviews.

However, we found two simulation studies on the effect of KI on thyroid irradiation [29, 30]. These studies suggest that KI is highly effective when administered 48 hours before and within two hours after exposure to radioiodine release. KI administration 48 hours before exposure to radioiodine release results in an almost complete blocking of radioiodine uptake. However, intake of KI 96 hours before exposure to radioiodine release has no protective effect [30]. In line with our results, these studies report a protective effect of KI intake after exposure to radioiodine release. The simulation studies report that intake of KI within two hours after exposure to radioiodine release results in a blockade of ca. 80% [29, 30]. The review authors consider this as important additional evidence.

Authors' conclusions

Implications for practice

The results suggest that KI administration following a nuclear accident could be an effective means of reducing the risk of thyroid cancer, specifically in children. There is no evidence on the outcomes hypothyroidism and benign thyroid nodules, but the risk of occurrence of ATMA and TgAB could be reduced when subjects take KI in case of a nuclear accident.

Implications for research

Further studies of good quality are necessary to provide an evidence base for the effects of KI in case of nuclear accident on health outcomes. These studies should investigate the effects in subgroups, i.e. pregnant women. In addition, the dosage and the timing of the intervention seem to be relevant for the effectiveness of KI on thyroid blockade. Therefore, future research should consider the timing and dosage when investigating effects of KI after release of radioiodine on health outcomes. Hypothyroidism and benign thyroid nodules should be primary outcomes in future research on the effectiveness KI after a nuclear accident.

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Competing interests

The authors declare that they have no competing interests.

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Appendices

Appendix I: MEDLINE/PubMed Search

Block 1: health conditions

Search name	Search query	Type of search	Results
1A(1)	"thyroid gland"[MeSH Terms] OR "hypothyroidism"[MeSH Terms] OR "thyroid diseases"[MeSH Terms] OR "thyroid neoplasms"[MeSH Terms] OR "neoplasms, radiation-induced"[MeSH Terms] OR "radiation dosage"[MeSH Terms] OR "radiation injuries"[MeSH Terms] OR "dose-response relationship, radiation"[MeSH Terms]	MeSH major & sub-terms	268.837
1B	((thyroid*[Title/Abstract]) AND dysfuntion*[Title/Abstract] OR abnormalit*[Title/Abstract] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR tumor[Title/Abstract] OR tumour[Title/Abstract] OR tumors[Title/Abstract] OR tumours[Title/Abstract] OR nodul*[Title/Abstract] OR carcinogen*[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignanc*[Title/Abstract] OR medullar*[Title/Abstract] OR metastases[Title/Abstract] OR metastasi*[Title/Abstract] OR enlarged[Title/Abstract] OR disease*[Title/Abstract] OR hypothyroidism[Title/Abstract]))	keyword TI/AB	85.439
1	1A(1) OR 1B		292.436

Block 2: intervention(s)

Search name	Search query	Type of search	Results
2A(1)	"Potassium Iodide"[Mesh] OR "Iodine Radioisotopes"[Mesh]	MeSH major terms	50.555

2B	("ITB" OR "iodine thyroid blocking" OR "potassium iodide" OR "Iodine Radioisotope*" OR "KI" OR "sodium iodide" OR ((blockade* OR blocking OR administration) AND iodine) OR "stable iodine" OR ((prophylaxis OR prophylactic* OR "prophylactic agent*") AND (iodine* OR iodide*)))	keyword	83.987
2	2A(1) OR 2B		124.533

Block 3: occurrence/location

Search name	**Search query**	**Type of search**	**Results**
3A	"Radioactive Hazard Release"[Mesh] OR "Radioactive Fallout"[Mesh] OR "Nuclear Warfare"[Mesh] OR "Nuclear Reactors"[Mesh] OR "Chernobyl Nuclear Accident"[Mesh] OR "Nuclear Power Plants"[Mesh] OR "Fukushima Nuclear Accident"[Mesh]	MESH major terms	15.430
3B(3)	((Nuclear* OR atomic OR reactor* OR radioactive* OR radiation OR radiological*) AND (accident* OR warfare OR contaminat* OR exposure* OR fallout OR meltdown OR disaster* OR catastrophe*)) OR ((Belarus OR chernobyl OR Chornobyl OR Hiroshima OR Fukushima OR Gomel OR Homel OR Ukraine OR Minsk OR "3 mile" OR "three mile" OR Nagasaki OR Pripyat OR Poland OR Russia OR USSR OR "Soviet Union" OR Japan) AND (accident* OR warfare OR contaminat* OR exposure* OR fallout OR meltdown OR disaster* OR catastrophe*))	keyword	175.763
3	3A OR 3B(3)		177.762

Limits: publication types, human studies

Search name	**Search query**	**Results**
4A	"case reports"[Publication Type]	1.724.784
4B	("case reports"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])	1.908.867

4C	"animals"[Mesh]	17.833.169
4D	"humans"[Mesh]	13.824.418

Summary & results

Search name (Saved in PubMed & EndNote)	**Results**
1 AND 2 AND 3	1.321
1 AND 2 AND 3 (AND) NOT 4A	1.240
1 AND 2 AND 3 (AND) NOT 4B	1.225
1 AND 2 AND 3 (AND) NOT 4A (AND) NOT 4C	47
1 AND 2 AND 3 (AND) NOT 4B (AND) NOT 4C	47
1 AND 2 AND 3 (AND) NOT 4A AND 4D	1.038
1 AND 2 AND 3 (AND) NOT 4B AND 4D	1.023

Appendix II: EMBASE search

Block 1: health conditions

Search name	Search query	Type of search	Results
1A	("thyroid gland" or hypothyroidism or "thyroid disease" or "thyroid tumor" or "radiation induced neoplasm" or "radiation dose" or "radiation injury" or "radiation response").sh.	EMTREE headings & subheadings	200.489
1B	(thyroid* and (dysfuntion* or abnormalit* or cancer* or tumo?r* or nodul* or carcinogen* or carcinoma* or malignanc* or medullar* or metastases or metastasi* or enlarged or disease* or hypothyroidism)).ti,ab.	keyword TI/AB	89.540
1	1A OR 1B		250.074

Block 2: intervention(s)

Search name	Search query	Type of search	Results
2A	("potassium iodide" or "radioactive iodine").sh.	EMTREE headings & subheadings	13.298
2B	("ITB" or "iodine thyroid blocking" or "potassium iodide" or "Iodine Radioisotope*" or "KI" or "sodium iodide" or ((blockade* or blocking or administration) and iodine) or "stable iodine" or ((prophylaxis or prophylactic* or "prophylactic agent*") and (iodine* or iodide*))).mp.	mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword	71.537
2	2A OR 2B		79.961

Block 3: occurrence/location

Search name	Search query	Type of search	Results
3A	("nuclear accident" or "radioactive waste" or "atomic warfare" or "Nuclear Reactor" or "Chernobyl accident" or "Nuclear Power Plant" or "Fukushima Nuclear Accident").sh.	EMTREE headings & subheadings	15.174
3B	(((Nuclear* or atomic or reactor* or radioactive* or radiation or radiological*) and (accident* or warfare or contaminat* or exposure* or fallout or meltdown or disaster* or catastrophe*)) or ((Belarus or chernobyl or Chornobyl or Hiroshima or Fukushima or Gomel or Homel or Ukraine or Minsk or "3 mile" or "three mile" or Nagasaki or Pripyat or Poland or Russia or USSR or "Soviet	mp=title, abstract, heading word, drug trade name, original title, device manufacturer,	206.045

	Union" or Japan) and (accident* or warfare or contaminat* or exposure* or fallout or meltdown or disaster* or catastrophe*))).mp.	drug manufacturer, device trade name, keyword	
3	3A OR 3B		210.269

Limits

Search name	Search query	Results
4	elsevier.cr.	15.768.140

Summary & results

Search name	Results
1 AND 2 AND 3	1.339
1 AND 2 AND 3 AND 4	902

Translation of subject headings from MeSH to EMTREE terms

Block 1

MeSh Term	EMTREE Term
thyroid gland	thyroid gland
hypothyroidism	hypothyroidism
thyroid diseases	thyroid disease
Thyroid neoplasms	**thyroid tumor**
neoplasms, radiation-induced	radiation induced neoplasm
radiation dosage	radiation dose
radiation injuries	radiation injury
dose-response relationship, radiation	**radiation response**

Block 2

MeSh Term	EMTREE Term
Potassium Iodide	potassium iodide
Iodine Radioisotopes	**radioactive iodine**

Block 3

MeSh Term	EMTREE Term
Radioactive Hazard Release	**Nuclear accident**
Radioactive Fallout	**Radioactive waste**
Nuclear Warfare	**atomic warfare**
Nuclear Reactors	Nuclear Reactor
Chernobyl Nuclear Accident	**Chernobyl accident**
Nuclear Power Plants	Nuclear Power Plant
Fukushima Nuclear Accident	Fukushima Nuclear Accident

Appendix III: Excluded studies

Reason for Exclusion	Study
Clincial (experimental) study	Blum M, Eisenbud M. Reduction of thyroid irradiation from 131-I by potassium iodide. JAMA. 1967;200(12):1036-40. Epub 1967/06/19. PubMed PMID: 5337789.
Clincial (experimental) study	Sternthal E, Lipworth L, Stanley B, Abreau C, Fang SL, Braverman LE. Suppression of thyroid radioiodine uptake by various doses of stable iodide. N Engl J Med. 1980;303(19):1083-8. Epub 1980/11/06. doi: 10.1056/nejm198011063031903. PubMed PMID: 7421914.
Clincial (experimental) study	Ribela MT, Marone MM, Bartolini P. Use of radioiodine urinalysis for effective thyroid blocking in the first few hours post exposure. Health Phys. 1999;76(1):11-6. Epub 1999/01/12. PubMed PMID: 9883942.
Clincial (experimental) study	Takamura N, Hamada A, Yamaguchi N, Matsushita N, Tarasiuk I, Ohashi T, et al. Urinary iodine kinetics after oral loading of potassium iodine. Endocr J. 2003;50(5):589-93. Epub 2003/11/14. PubMed PMID: 14614215.
Clincial (experimental) study	Takamura N, Nakamura Y, Ishigaki K, Ishigaki J, Mine M, Aoyagi K, et al. Thyroid blockade during a radiation emergency in iodine-rich areas: effect of a stable-iodine dosage. J Radiat Res. 2004;45(2):201-4. Epub 2004/08/12. PubMed PMID: 15304961.
Clincial (experimental) study	Hanscheid H, Reiners C, Goulko G, Luster M, Schneider-Ludorff M, Buck AK, et al. Facing the nuclear threat: thyroid blocking revisited. J Clin Endocrinol Metab. 2011;96(11):3511-6. Epub 2011/08/26. doi: 10.1210/jc.2011-1539. PubMed PMID: 21865356.
Clincial (experimental) study	Cuddihy RG. Thyroidal iodine-131 uptake, turnover and blocking in adults and adolescents. Health Phys. 1966;12(8):1021-5. Epub 1966/08/01. PubMed PMID: 6013191.
Clincial (experimental) study	Kunii, Y., et al. (2012). "The effect of potassium iodide on radioactive iodine uptake of the healthy Japanese." European Thyroid Journal 1: 188.
Simulation study	Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by 131I from radioactive fallout. Health Phys. 2000;78(6):660-7. Epub 2000/06/01. PubMed PMID: 10832925.
Simulation study	Jang M, Kim HK, Choi CW, Kang CS. Age-dependent potassium iodide effect on the thyroid irradiation by 131I and 133I in the nuclear emergency. Radiat Prot Dosimetry. 2008;130(4):499-502. Epub 2008/03/14. doi: 10.1093/rpd/ncn068. PubMed PMID: 18337292.
Simulation study	Jang M, Kim HK, Choi CW, Kang CS. Thyroid dose estimation with potassium iodide (KI) administration in a nuclear emergency. Radiat Prot Dosimetry. 2008;132(3):303-7. Epub 2008/12/05. doi: 10.1093/rpd/ncn299. PubMed PMID: 19054795.
Simulation study	Meck RA, Chen MS, Kenny PJ. Criteria for the administration of KI for thyroid blocking of radioiodine. Health Phys.

	1985;48(2):141-57. Epub 1985/02/01. PubMed PMID: 3882630.
Dosimetry study	Goulko GM, Chumak VV, Chepurny NI, Henrichs K, Jacob P, Kairo IA, et al. Estimation of 131I thyroid doses for the evacuees from Pripjat. Radiat Environ Biophys. 1996;35(2):81-7. Epub 1996/05/01. PubMed PMID: 8792454.
Dosimetry study	Balonov M, Kaidanovsky G, Zvonova I, Kovtun A, Bouville A, Luckyanov N, et al. Contributions of short-lived radioiodines to thyroid doses received by evacuees from the Chernobyl area estimated using early in vivo activity measurements. Radiat Prot Dosimetry. 2003;105(1-4):593-9. Epub 2003/10/07. PubMed PMID: 14527033.
Dosimetry study	Nedveckaite T, Filistovic V, Mastauskas A, Thiessen K. Thyroid dosimetry in the western trace of the Chernobyl accident plume. Radiat Prot Dosimetry. 2004;108(2):133-41. Epub 2004/02/24. doi: 10.1093/rpd/nch016. PubMed PMID: 14978293.
Dosimetry study	Stepanenko VF, Voilleque PG, Gavrilin YI, Khrouch VT, Shinkarev SM, Orlov MY, et al. Estimating individual thyroid doses for a case-control study of childhood thyroid cancer in Bryansk Oblast, Russia. Radiat Prot Dosimetry. 2004;108(2):143-60. Epub 2004/02/24. doi: 10.1093/rpd/nch017. PubMed PMID: 14978294.
Dosimetry study	Drozdovitch V, Minenko V, Khrouch V, Leshcheva S, Gavrilin Y, Khrutchinsky A, et al. Thyroid dose estimates for a cohort of Belarusian children exposed to radiation from the Chernobyl accident. Radiat Res. 2013;179(5):597-609. Epub 2013/04/09. doi: 10.1667/rr3153.1. PubMed PMID: 23560632; PubMed Central PMCID: PMCPMC3682838.
Missing outcome	Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. The American journal of medicine. 1993;94(5):524-32. Epub 1993/05/01. PubMed PMID: 8498398.
Missing outcome	Szybinski Z, Nauman J, Gembicki M, Rybakowa M, Huszno B, Golkowski F, et al. Principles, main goals and methods of the nationwide program: "investigations on iodine deficiency and model of iodine prophylaxis in Poland". Endokrynol Pol. 1993;44(3):235-48. Epub 1993/01/01. PubMed PMID: 8055793.
Missing intervention	Hatch M, Brenner A, Bogdanova T, Derevyanko A, Kuptsova N, Likhtarev I, et al. A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to iodine-131 from Chernobyl fallout. J Clin Endocrinol Metab. 2009;94(3):899-906. Epub 2008/12/25. doi: 10.1210/jc.2008-2049. PubMed PMID: 19106267; PubMed Central PMCID: PMCPMC2681280.
Missing intervention	Ivanov, V. K., et al. (2006). "Radiation-epidemiological studies of thyroid cancer incidence among children and adolescents in the Bryansk oblast of Russia after the Chernobyl accident (1991-2001 follow-up period)." Radiat Environ Biophys 45(1): 9-16.
Note/Editorial, dossier, policy review; no original data	Volf V. Thyroid protection after a nuclear reactor accident. Lancet. 1986;2(8501):284. Epub 1986/08/02. PubMed PMID: 2874306.
Note/Editorial,	Martin JA, Jr. Potassium iodide: predistribution or not? The real

dossier, policy review; no original data	emergency preparedness issue. Health Phys. 1985;49(2):287-9. Epub 1985/08/01. PubMed PMID: 4019199.
Note/Editorial, dossier, policy review; no original data	Yalow RS. Potassium iodide: effectiveness after nuclear accidents. Science. 1982;218(4574):742. Epub 1982/11/19. PubMed PMID: 7134970.
Note/Editorial, dossier, policy review; no original data	Vernis M, Hindie E, Galle P. [Protection of the thyroid in children and fetuses in case of nuclear accident]. Arch Pediatr. 1997;4(5):473-9. Epub 1997/05/01. PubMed PMID: 9230999.
Note/Editorial, dossier, policy review; no original data	Protecting children in a radiation disaster. Child Health Alert. 2003;21:1-2. Epub 2003/05/30. PubMed PMID: 12772690.
Note/Editorial, dossier, policy review; no original data	Stezhko VA, Buglova EE, Danilova LI, Drozd VM, Krysenko NA, Lesnikova NR, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods. Radiat Res. 2004;161(4):481-92. Epub 2004/03/25. PubMed PMID: 15038762.
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Appendix IV: GRADE evidence profile

Is the administration of KI preferable to no treatment in people exposed to radioiodine release in the environment to reduce the risk of thyroid cancer, hypothyroidism and benign thyroid nodules?

Number of studies	Design	Quality assessment					Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Other	KI	No KI	Relative (95% CI)	Absolute (95% CI)	
ATMA											
1	Cross-sectional study	Serious concern[a]	No serious concern	No serious concern	Very serious concern[b,c]	None	22/169 (13.0)	114/816 (14.0)	OR 0.92 (0.56 to 1.50)	10 fewer per 1000 (from 70 fewer to 50 more)	Very low
TgAB											
1	Cross-sectional study	Serious concern[a]	No serious concern	No serious concern	Very serious concern[b,c]	None	17/169 (10.1)	107/816 (13.1)	OR 0.74 (0.43 to 1.27)	30 fewer per 1000 (from 80 fewer to 20 more)	Very low
Thyroid Cancer											
1	Analytic cohort	No serious concern	No serious concern	No serious concern	Serious concern[b]	None	12/ 18154 (0.1)[*]	50/ 51674 (0.1)[*]	OR 0.68 (0.36 to 1.28)[*]	0 fewer per 1000 (from 0 fewer to 0 more)[*]	Low
2	Case-control study	Serious concern[a]	Serious concern[d]	No serious concern	Serious concern[b]	None	104/549 (18.9)[#]	313/1443 (21.7)[#]	OR 0.84 (0.66 to 1.08)[#]	30 fewer per 1000 (from 70 fewer to	Very low

										10 more)[#]	

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR: odds ratio.

[a] No control for confounding.

[b] Few events.

[c] Wide confidence intervals.

[d] Point estimates vary widely across studies and confidence intervals show no overlap.

[*] Data are based on person years.

[#] Data are based on controls and cases.

Appendix V: Characteristics of included studies

Study	**Zarzycki et al. 1994**
Aim	The aim of the study was the estimation of the effects, possible side-effects and immunological reactions after the mass iodine prophylaxis following the Chernobyl nuclear disaster.
Methods	From the whole population of 11657 persons exposed to identical amounts of radioactive fallout, 1457 subjects (12.98%), born between 01.01.1936 and 31.12.1985, were randomly chosen for the study.
Participants	1457 subjects, aged 6 - 5 5 yrs, filled in the questionnaires and in 1191 of them the titres of antithyroid antibodies (TA) including ATMA - Anti-Human Thyroid Membrane Antibodies and TGAb - Anti-Thyreoglobulin Antibodies were estimated. The study consists of children up to 10 yrs (92 boys and 93 girls), and from 11 to 16 yrs (72 boys and 72 girls), youths 17-19yrs (28 males and 33 females), and two groups of adults – 503 individuals from 20 to 40 yrs (221 males and 288 females) and 558 subjects over 40 yrs (228 males and 320 females).
Interventions	Administration of iodine prophylaxis versus no administration of iodine prophylaxis following the Chernobyl nuclear disaster
Outcome	Antithyroid antibodies (TA) including ATMA - Anti-Human Thyroid Membrane Antibodies and TGAb - Anti-Thyreoglobulin Antibodies
Notes	Results are not available for subgroups (males vs. females; age-groups)

Study	**Cardis et al. 2005**
Aim	Authors carried out a population-based case – control study of thyroid cancer in Belarus and the Russian Federation to evaluate the risk of thyroid cancer after exposure to radioactive iodine in childhood and to investigate environmental and host factors that may modify this risk.
Methods	The study was designed as a population-based case-control study of thyroid cancer in young people. It was carried out in the regions of Belarus and the Russian Federation that were most contaminated by fallout from the Chernobyl accident. Case patients were diagnosed with histologically verified thyroid carcinoma and underwent surgery in Belarus or the Russian Federation. Control subjects were randomly drawn from the birth registry centralized at the region level in all regions except for Kaluga and Orel, where access to the birth registry records was denied by local administrative authorities. In these regions, therefore, control subjects were selected from the records of the computerized medical insurance system, which covers virtually the entire population.
Participants	276 case patients and 1300 control subjects who resided in the Gomel and Mogilev administrative regions (i.e., oblasts) of Belarus or the Tula, Orel, Kaluga, and Bryansk administrative regions of the Russian Federation and were aged younger than 15 years at the time of the Chernobyl accident. The case patients were diagnosed with histologically verified thyroid carcinoma between January 1, 1992 [to avoid overlap with a previous case-control study in Belarus], and December 31, 1998, and underwent surgery in Belarus or the Russian Federation.
Interventions	Consumption of potassium iodide as antistrumin (a preparation that was used in the former Soviet Union for goiter prophylaxis and that was distributed, mainly in Belarus, to children evacuated after the Chernobyl accident) vs no consumption of potassium iodide The usual doses for goiter prophylaxis were as follows: 0.5 mg every 15 days for children aged 1 – 3 years, 0.5 mg weekly for children aged 3 – 7 years, and 1 mg weekly for children older than 7 years
Outcome	Risk of developing thyroid cancer

Notes	Missing relevant data were obtained from study's authors.

Study	**Brenner et al. 2011**
Aim	To evaluate the dose–response relationship for incident thyroid cancers diagnosed as a result of second to fourth screening examinations based on up to 9 years of follow-up.between 1998 and 2007.
Methods	This cohort study examined several unresolved issues using prospective data from a cohort composed of approximately 12,500 individuals who were < 18 years of age when the accident occurred and had individual radioactivity measurements taken within 2 months after the accident. In brief, the cohort includes individuals with direct thyroid radioactivity measurements made in May or June 1986 who were < 18 years of age on 26 April 1986 and resided in selected areas in the neighboring Chernihiv, Zhytomyr, or Kyiv oblasts of Ukraine in 1998.
Participants	Of 32,385 individuals originally selected for the study, 10,307 (31.8%) could not be traced primarily because of the long interval between the accident and the start of screening, as well as high mobility of this young cohort; 2,466 (7.6%) were traced but were not eligible or available to participate; and 6,369 (19.7%) were traced but refused to participate or failed to attend the screening, resulting in 13,243 (40.9%) individuals who were screened for the first time between 1998 and 2000. After additional exclusions described elsewhere, analysis of thyroid cancer prevalence was based on 13,127 individuals. In the present analysis, we also excluded 45 individuals who were diagnosed with thyroid cancer as the result of the first screening examination, 3 individuals who were found to have thyroid aplasia, and 566 individuals (4.3%) who were considered lost to follow-up because they participated in only the first screening examination. We included 1 individual who was diagnosed with incident thyroid cancer 8 years after the first examination but was previously excluded from the analyses because of incomplete data at baseline.

	This resulted in a total of 12,514 individuals included in the present analysis.
Interventions	Intake of iodine prophylaxis in May–June 1986 (yes/no)
Outcome	Thyroid cancer
Notes	-

Study	**Bandurska-Stankiewicz et al. 2010**
Aim	The aim of the study was to investigate if the Chernobyl atomic plant disaster had an influence on thyroid cancer incidence in Olsztyn province, Poland.
Methods	The prospective study on thyroid cancer incidence was conducted in Olsztyn province from 1 January 1994 to 31 December 2003 within its former administrative boundaries in spite of the new administrative division of Poland which became effective as of 1 January 1999. The study of selected risk factors affecting changes in thyroid cancer incidence was conducted among patients entered in the standardized register in the 1994-2003. Patients completed the questionnaires during follow-up outpatient clinic visits in the Endocrinology Outpatient Clinic in Olsztyn. In cases of severe disability or change of place of residence answers were obtained by mail, or in some cases, by phone.
Participants	The study includes 297 patients with thyroid carcinoma. The control group consists of 589 healthy subjects chosen according to age and place of residence, who completed the "Questionnaire for patients with thyroid gland carcinoma" apart from the questions concerning the basic disease.

Interventions	Iodine prophylaxis (Lugol's soluation) during the Chernobyl accident
Outcome	Thyroid cancer
Notes	-