Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: A meta-analysis

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Abstract

Radioiodine (131I) is widely used for diagnosis and treatment of benign thyroid diseases. Observational studies have not been conclusive about the carcinogenic potential of 131I and we therefore conducted a meta-analysis. We performed a literature search till September 2011 which included 131I as a diagnostic or treatment modality (131I for treatment of thyroid cancer was excluded). Data on 64 different organ or organ group subsets comprising of 22,029 exposed subjects in the therapeutic cohorts and 24,799 in the diagnostic cohorts in seven studies were included. Outcome was pooled as the relative risk (RR) using both standard and bias adjusted methods. Quality assessment was performed with a study specific instrument. No increase in overall (RR 1.06, 95 % CI 0.94 - 1.19), main organ group or combined organ group (four groups known to concentrate 131I; RR 1.11, 95 % CI 0.94-1.31) risks was demonstrable. Individual organs, demonstrated a higher risk for kidney (RR 1.70, 95 % CI 1.15 - 2.51) and thyroid (RR: 1.99, 95 % CI 1.22 - 3.26) cancers with a strong trend for stomach cancer (RR 1.11; 95% CI 0.92 - 1.33). A thyroid dose effect was seen for diagnostic doses. While there is no increase in the overall burden of cancer, an increase in risk to a few organs is seen that requires substantiation. The possible increase in thyroid cancer risk following diagnostic 131I use should no longer be of concern given that it has effectively been replaced by as the use of 99mTc-pertechnetate.

Key words: Meta-analysis, carcinogenesis, radioiodine, benign thyroid diseases
**Introduction**

Among the many radionuclides used in nuclear medicine, radioiodine-131 (131I) (physical half-life~8 days), plays an important role and has been used successfully for seven decades. Since its introduction in 1941,(Hertz and Roberts, 1946, Chapman and Evans, 1946) it is likely that millions of patients with benign thyroid disease have been administered therapeutic or diagnostic activities. The ease of its administration,(Ross, 2011) lack of significant adverse effects,(Read et al., 2004) and low cost,(Ross, 2011) have prompted such wide spread use even though there still remains some uncertainty in terms of its carcinogenic potential.(Solomon et al., 1990, Glinoer et al., 1987, Walsh, 2000, Tominaga et al., 1997, Lucignani, 2007) In favour of 131I therapy, however, is the fact that the radiation dose to the thyroid is so high that in most cases a large mass of the thyroid gland is ablated and absorbed dosages to other organs are very low.(ICRP 1987) It is however only in Graves’ disease that 131I treatment achieves such high tissue doses in the thyroid that the thyroid epithelial cells are destroyed. With toxic nodules or toxic goitre, the attempt is to achieve lethal tissue doses in the hyperactive tissue while trying to avoid lethal doses in the “healthy” tissue. So there is a possibility that we do induce carcinogenesis in the remaining gland. This is in contrast to external radiotherapy where doses are in the intermediate range to surrounding organs resulting in sub-lethal cellular damage. Although the carcinogenic effects of moderate doses of therapeutic X-radiation and gamma radiation are fairly well described,(Ron, 2003) it is likely that risks after 131I are much less given that the thyroid concentrates most of the radioiodine and doses to most organs are very small (0.04 to 0.14 mGy/MBq)(Zanzonico, 2000) and delivered over several days.

Several long term cohort studies from groups in Sweden, (Holm et al., 1991) England,(Franklyn et al., 1999) Finland,(Metso et al., 2007) and the US(Hoffman et al., 1982,
Goldman et al., 1988) that have investigated the relationship between cancer risk following therapeutic use of 131I in benign thyroid disease provides conflicting results. For example, studies report an increase,(Holm et al., 1991, Metso et al., 2007) a decrease(Franklyn et al., 1999) or no change(Hoffman et al., 1982) in overall cancer risk. Also, reports of increased breast(Metso et al., 2007), kidney(Holm et al., 1991) and thyroid(Hoffman et al., 1982, Franklyn et al., 1999) cancer risk are contradicted by other reports of breast,(Hoffman et al., 1982, Goldman et al., 1988, Holm et al., 1991, Franklyn et al., 1999) kidney(Hoffman et al., 1982, Metso et al., 2007) or thyroid cancers.(Metso et al., 2007, Holm et al., 1991) A recent overview of this topic by Verburg et al.(Verburg et al., 2011) suggests that the evidence is not conclusive in favour of increased risk. However, since individual studies on their own are unlikely to answer this important question, we decided to embark on a meta-analysis of the evidence available. Also, cancer is a rare outcome, so in order to estimate the incidence of cancers after exposure to 131I, long periods of follow up and a large population is required that could be addressed by meta-analysis.

**Methods**

**Data sources & eligibility criteria**

The medical literature, till September 2011, was searched for articles reporting on the diagnostic or therapeutic use of 131I in benign thyroid diseases and the development of cancer. The references of selected articles were cross-checked for further studies, other language publications were translated where deemed necessary and details of the search strategy and databases searched are in Supplementary Appendix I. Inclusion was limited to human studies with exclusions made for 131I exposure in thyroid cancer (therapeutic or diagnostic), in nuclear accidents, and reports of a non-analytic observational design.

**Data abstraction and quality assessment**
A data extraction table was completed for each study (see results). A methodological quality checklist was developed based on a modification of the general checklist created by Doi and Thalib (Doi and Thalib, 2008) (see Supplementary Appendix II). The maximum score was ten points and quality was assessed by two independent reviewers with any discrepancies addressed by consensus.

**Statistical analysis**

The primary outcome was the relative risk (RR) or the standardized incidence ratio (SIR) in those exposed to radioiodine compared to those not exposed or a standardized population respectively. The SIR was defined as the number of cases observed in the study population divided by the number of cases that would be expected in a standardized population. The RR was defined as the risk of developing a cancer within the follow-up time compared to a control group. SIR and RR were stratified by cancer site. The standardized incidence ratio was used as an estimate of the RR and we report the pooled RR in this meta-analysis. The latter was justified because both the prevalence of cancer and the RR for cancer is expected to be low. (Chaturvedi et al., 2008) Heterogeneity was determined to be present when the calculated value of \( \tau^2 \) was greater than zero and/or the Q-statistic was significant at \( P < 0.1 \). (Takkouche et al., 1999) Studies were pooled using the quality-effects (QE) model (Doi and Thalib, 2008, Doi et al., 2011) to take advantage of both bias adjustment (Doi et al., 2011) and additional weighting by the incidence of cancers (AIHW, 1998) in the population at large because incidence differs widely by cancer type and failure to consider this would not reflect overall burden of risk. This sort of weighting has been applied by us previously, (Jamal et al., 2012) and though the latter is not possible with routine models of meta-analysis, we also report a sensitivity analysis using the conventional fixed effects model for homogenous studies and random effects model for heterogeneous studies.
Finally, a subgroup analysis was conducted by computing the ratios of SIRs (Morris and Gardner, 1988) (RSIR & 95%CI) in subgroups (defined by duration of follow-up, dose/activity of 131I and age at the time of exposure; see Supplementary Appendix III). To check for publication bias, funnel plot asymmetry could not be used as we had too few studies in each group. However, an exclusion sensitivity analysis was performed to check the impact of individual studies by excluding each study and calculating the overall effects again. All analyses were done using MetaXL version 1.2 (http://www.epigear.com).

Results

2929 unique abstracts were reviewed and the full text of 24 studies were retrieved (Figure 1). 17 of these were then excluded because they were not found to address 131I use (N = 3), (Berlin and Wasserman, 1976, Hoffman et al., 1984, Mellemgaard et al., 1998) did not report effect sizes (RR or SIR) (Munoz et al., 1978), were descriptive studies (N = 7) (Listewnik et al., 2010, Angusti et al., 2000, Dobyns et al., 1974, Freitas et al., 1979, Ozaki et al., 1994, Pochin, 1960, Spencer et al., 1983) or had overlapping datasets (N = 6). (Holm et al., 1980, Holm et al., 1988, Hall and Holm, 1995b, Hall and Holm, 1995a, Saenger et al., 1968, Hall et al., 1996) Seven studies were finally selected into this meta-analysis. (Hoffman et al., 1982, Goldman et al., 1988, Metso et al., 2007, Dickman et al., 2003, Hahn et al., 2001, Franklyn et al., 1999, Holm et al., 1991)

Characteristics of the included studies

We included 64 different organ or organ group subsets in five therapeutic (Hoffman et al., 1982, Goldman et al., 1988, Franklyn et al., 1999, Holm et al., 1991, Metso et al., 2007) and two diagnostic studies. (Hahn et al., 2001, Dickman et al., 2003) There were 22029 exposed subjects in the therapeutic cohorts and 24799 in the diagnostic cohorts (see Table 1). Although the data source in the Dickman et al. study (Dickman et al., 2003) overlapped with
the Holm et.al. study (Holm et al., 1991), the focus was diagnostic in the former study, and patients with therapeutic use of 131I were excluded. The population in these studies originated from the US, Sweden, Finland, UK, and Germany. The mean follow-up time varied from 9.8 to 27 years. RRs were estimated in three studies (Metso et al., 2007, Hoffman et al., 1982, Hahn et al., 2001) while the other four studies reported the SIRs. (Goldman et al., 1988, Holm et al., 1991, Franklyn et al., 1999, Dickman et al., 2003) The quality scores of studies ranged from five to eight out of ten. All of seven studies were retrospective (see Supplementary Appendix IV for further details regarding each study). The diagnostic studies reported only on thyroid cancer risk.

**Ascertainment of cancer diagnosis**

In all seven studies, cancer was the main endpoint retrospectively ascertained. Three studies (Hoffman et al., 1982, Goldman et al., 1988, Hahn et al., 2001) used either questionnaires, telephone interview, autopsy reports (if available) and medical records from the Cooperative Thyrotoxicosis Therapy Follow-up Study.

Four studies (Franklyn et al., 1999, Holm et al., 1991, Metso et al., 2007, Dickman et al., 2003) used more robust methods as data was retrieved from national cancer registries to identify cancer from Sweden, (Holm et al., 1991, Dickman et al., 2003) Finland, (Metso et al., 2007) and the UK. (Franklyn et al., 1999)

**Quantitative synthesis of data (therapeutic use only (a-c))**

*a. Overall cancer risk*

Seven main organ groups from five studies (Hoffman et al., 1982, Goldman et al., 1988, Franklyn et al., 1999, Holm et al., 1991, Metso et al., 2007) (Figure 2) suggests no increase in cancer risk overall (RR 1.06 (95%CI: 0.94-1.19; Figure 2a). Results were
sensitive to exclusion of the Franklyn study, (Franklyn et al., 1999) after which pooled risk of cancer increased (RR 1.13, 95% CI: 1.03-1.24; Figure 2b). Conventional weighting methods (no population or bias weights) concurred RR 1.03 (95% CI 0.94-1.13) compared with RR 1.12 (95% CI 1.04-1.20) when the Franklyn study (Franklyn et al., 1999) was excluded.

b. Organ groups that concentrate 131I

Four organ groups known to concentrate radioiodine (digestive organs and peritoneum; lip, oral cavity, and pharynx; genitourinary organs; and thyroid), revealed no increase in risk (RR 1.11, 95% CI 0.94-1.31). Results were sensitive to exclusion of the Franklyn study (Franklyn et al., 1999) after which risk increased (RR 1.17, 95% CI 1.06-1.30). The latter was mainly because the Franklyn study (Franklyn et al., 1999) had protective estimates for digestive and genitourinary organs. Similar results were obtained with conventional weighting (RR 1.06 (95% CI 0.98-1.13) compared to RR 1.12 (95% CI 1.04-1.21) after removal of the Franklyn (Franklyn et al., 1999) study).

c. Individual organ groups

Seven organ groups (Figure 2) from five papers did not demonstrate an increase in cancer risk (Supplementary Appendix Vb). Digestive and respiratory organs groups were, however, sensitive to exclusion of the Franklyn study, (Franklyn et al., 1999) resulting in borderline significance in favour of increased risk (lower confidence limit of 1.01-1.03, Figure 2b). Conventional weighting methods suggest a slight difference in direction of the pooled estimate for digestive organs & peritoneum; lip, oral cavity, & pharynx; and bone, connective tissues, skin & breast although none were significant and were most likely random changes (see Supplementary Appendix Vc).
d. Individual organs

Nine individual organs (salivary glands, breast, kidney, bladder, lymphoma, leukaemia, pancreas, stomach and thyroid) in five studies reveal a higher risk of only kidney and thyroid cancers while stomach cancer demonstrated a non-significant trend (Supplementary Appendix Vb).

The kidney cancer RR was 1.70 (95%CI: 1.15-2.51) from three studies. Exclusion of the Metso study (Metso et al., 2007) decreases the significance of the kidney cancer result and puts most of the weight on the Holm study (Holm et al., 1991).

The thyroid cancer risk (RR: 1.99, 95%CI 1.22-3.26) was mitigated by removal of the Franklyn study (Franklyn et al., 1999) resulting in a RR of 1.58 (95%CI 0.91-2.75). These studies had less than 10 observed cases of thyroid cancer (Franklyn et al., 1999, Hoffman et al., 1982, Metso et al., 2007) and the Holm et al study (Holm et al., 1991) with 18 observed cases did not demonstrate increased risk. Conventional weighting methods concurred with these results (see Supplementary Appendix Vc).

Finally, the only two studies (Hahn et al., 2001, Dickman et al., 2003) of diagnostic 131I use (pooled separately) did not demonstrate an increase in thyroid cancer risk (RR = 1.06, 95% CI 0.62, 1.82). However, one of these studies was in children only (Hahn et al., 2001) while the other (Dickman et al., 2003) was predominantly undertaken in adults (only 7% were below the age of 20 years). The RR (or SIR) for thyroid cancer was 0.9 (CI 0.1 – 5.1) in childhood exposure versus 0.91 (CI 0.64 – 1.26) with adult exposure (excluding subjects with prior radiation therapy or referred for suspicion of a tumor). The risks in the adult study (Dickman et al., 2003) were significantly higher with prior radiation with (SIR 13.66; 95% CI 7.06 – 23.87) or without (SIR 7.67; 95% CI 3.96 – 13.40) referral for a thyroid tumor.
Stratification by time since exposure, age at exposure, absorbed dose and administered activity of 131I

To examine the effect of time since exposure, age at exposure and dose of 131I on cancer risk, we calculated the ratio of the SIR’s (RSIR) using data from three studies that used this effect size and reported subgroups. (Goldman et al., 1988, Hall et al., 1992, Dickman et al., 2003) This was done in lieu of a subgroup meta-analysis because there was not enough data to perform a stratified analysis.

Time since exposure to 131I had a significant effect only on stomach cancer with the ratio of SIRs of 1.77 (95%CI 1.03-3.53) and the >15 year SIR showing a statistically significant increase.

Thyroid dose after diagnostic administration and therapeutic activity administered were compared in two studies. (Hahn et al., 2001, Dickman et al., 2003) The diagnostic study (Dickman et al., 2003) demonstrated that the patients with an absorbed dose greater than 1 Gy had 2.82 times the SIR compared with patients with an absorbed dose of less than 0.25 Gy (ratio of SIRs 2.82, 95%CI: 1.22-14.89) although neither of the stratum specific SIR’s were significant. The therapeutic study (Goldman et al., 1988) reported that >10 mCi compared to no administration of 131I did not significantly alter SIR estimates.

Finally, there was no trend of increasing SIR of thyroid cancer as age at exposure to 131I for diagnostic use decreased (Dickman et al., 2003) (RSIR = 1.06; 95%CI: 0.44-2.40) when those 20-50 years old were compared with those >50 years old.

Discussion

Overall burden of cancer risk

Although case reports of several cancers (McCormack and Sheline, 1963, Kennedy and Fish, 1959, Bundi et al., 1977, Spencer et al., 1983, Munoz et al., 1978) after radioactive iodine treatment have raised question about the carcinogenesis of 131I, the evidence from this
meta-analysis is lacking. In exposed patients, there was no increase in cancer risk overall. Individual organ groups as well as a combination of organ groups (CG) known to concentrate radioiodine (salivary glands, digestive tract and urinary tract) did not also demonstrate an increased risk of cancer. Individual studies of overall (Holm et al., 1991, Metso et al., 2007) or CG (Hoffman et al., 1982) risks do report a slight increase in cancer but the overall burden of risk by our population weighted estimate as well as conventional models concurred suggesting that overall burden of risk was null.

**Thyroid**

Lack of an overall increase in burden of cancer risk is consistent with the low levels of organ doses expected from 131I exposure that remain far from reported dangerous threshold of between 100 and 1000 mGy (Kloos, 2011). This level of exposure is reached, after 131I administration, within the thyroid, but is thought to be less important because the thyroid is ablated and tissue does not remain for carcinogenesis to ensue. Also, while a significant risk of thyroid cancer has been observed after administration of therapeutic X-irradiation with doses as high as 60 Gy in childhood (Tucker et al., 1991, de et al., 1988) this has not been observed in several large cohort studies after use of a similar radiation absorbed dose of 131I for treatment of hyperthyroidism (Dobyns et al., 1974, Holm et al., 1980, Holm et al., 1991, Metso et al., 2007, Goldman et al., 1988, Angusti et al., 2000).

The two studies that demonstrate an increase in the risk of thyroid cancer (Franklyn et al., 1999, Hoffman et al., 1982) differ from the other studies. The Hoffman study (Hoffman et al., 1982) reports a RR of 9.1 but this result was based on three cases in the 131I group and one case in the control (surgical) group. (Hoffman et al., 1982) There was a tendency toward increased risk for women <40 years old and decreased risk with increasing age at exposure. (Hoffman et al., 1982) This result could have been biased by medical screening following treatment of hyperthyroidism, patient selection bias, choice of surgically treated
patients as control groups and limited observation time. In the case of the Franklyn study, (Franklyn et al., 1999) data on cancer incidence (for patients and controls) were drawn from different sources so bias was likely. Franklyn et. al. (Franklyn et al., 1999) compared site-specific data on cancer incidence from follow-up with data from England and Wales in preference to comparison with incidence from the study region because regional control data were incomplete and about 20% of patients had moved from the region before study completion. Indeed, after exclusion of the Franklyn study (Franklyn et al., 1999) our pooled estimate for thyroid cancer (RR 1.99; 95% CI 1.22-3.26) declines to non-significance (RR 1.58; 95% CI 0.91-2.75) and this is contrary to the protective trend seen for other cancers.

Overall, there is the problem of confounding by indication in studies that report increased risk since thyroid cancer is far more common in those with nodular thyroid disease (as compared to Graves') (Angusti et al., 2000) and also thyroid cancer, if associated with Graves' disease, is found more commonly in surgically treated patients than in patients after 131I therapy. (Behar et al., 1986) Indeed, under 20 year old individuals that did not presumably have nodular disease and who received 131I for Graves’ disease that were, followed-up for 36 years, revealed no cases of cancer of the thyroid. (Read et al., 2004) Also, stratification by duration of follow-up (Holm et al., 1991) did not result in a significant increase in the SIR for thyroid cancer.

Diagnostic 131I use had no increase in risk demonstrable and this concurs with several studies of diagnostic 131I use in children or adolescents. (Hahn et al., 2001, Hall et al., 1996, Holm et al., 1988, Dickman et al., 2003) There was also no increase in SIR when stratification by duration of follow-up or age at exposure was done. (Dickman et al., 2003) It has been estimated that for an adult, assuming a 15% uptake, a thyroid scan with 1.85-7.4 MBq 131I orally exposes the thyroid to 388-1554 mGy (SNM, 1999) and the Dickman study (Dickman et al., 2003) demonstrated an increased SIR when the dose was >1000 mGy as
compared to <250mGy. This might be of concern given that this was absorbed dose to a non-ablated thyroid gland. Nowadays however, it is much more common to use 75-370MBq 99mTc-pertechnetate i.v., which results in a much lower thyroid exposure, with the highest exposure being to the upper large intestine to the order of 5-23mGy.(SNM, 1999) While there is little evidence to suggest that the use of diagnostic 131I in adults is carcinogenic, additional data are needed to clarify the risks associated with childhood medical exposure.(Ron, 2003)

Other organs

Doses to other organs are quite low and an excess of cancers has never been detected for doses below 100mGy(Kloos, 2011) and after repeated X-ray examinations, a cancer excess is reported only for cumulative doses greater than about 500mGy.(Vaiserman, 2010) Suit et al have reviewed secondary carcinogenesis after radiation exposure and conclude that the factorial decrease in risk of radiation-induced secondary cancer would be greatest for reduction in dose levels below 2 Gy. This dose is not reached in any organ (other than the thyroid) after 131I therapy(Suit et al., 2007) and (apart from the stomach) parallels doses received from common medical imaging procedures ranging up to 20mGy (for chest/abdominal CT and coronary angiogram).

The highest non-thyroidal exposure is reported to be the stomach at about 0.41mGy/MBq(Zanzonico, 2000) averaging 250mGy.(Huysmans et al., 1996, Edmonds and Smith, 1986) Within the gastrointestinal system, ingested 131I is completely absorbed from the stomach into blood and does not pass through the other compartments of the gastrointestinal tract.(Zanzonico, 2000) Three studies (excluding Franklyn(Franklyn et al., 1999)) concur in terms of increasing trend for stomach cancer,(Holm et al., 1991, Hoffman et al., 1982, Metso et al., 2007) even though the meta-analysis of digestive tract cancer on the
whole revealed no increased risk, and neither does the meta-analysis of stomach cancer. The strongest effect was with the Metso study (Metso et al., 2007) (stomach cancer had 30 cases in the exposed group and a RR of 1.76). In addition, stratification by duration of follow-up revealed significant increases in the SIR for stomach cancer. (Holm et al., 1991) Data on the dependence of risk on radiation dose for stomach carcinogenesis in patients treated with radiation demonstrate that the slope for the stomach is significantly positive (Suit et al., 2007) and it might therefore be prudent to consider caution especially so in patients with a strong family history of gastric carcinoma. (Meyer, 1994)

Among other individual organs, we did find a higher risk of kidney cancer (RR 1.70). In terms of urinary cancers, others have found no increased risk to the bladder (Holm et al., 1991, Franklyn et al., 1999, Hoffman et al., 1982) though two studies (Metso et al., 2007, Holm et al., 1991) concur on renal cancer. Our pooled estimate for individual urinary organs suggests that the increased risk is mainly to the kidney. When we examined strata by duration of follow-up (Holm et al., 1991) the ratio of SIRs were not different from unity for kidney cancer. However, there were 90 cases of kidney cancer reported in three studies (Holm et al., 1991, Metso et al., 2007, Hoffman et al., 1982) and this raises concern. Fortunately, data from patients treated with radiation does suggest that the RR (radiotherapy to general population) as a function of dose up to 15Gy for the kidney is non-significantly positive and the curve for bladder is flat. (Suit et al., 2007) Both the latter observation and the smaller dose expected to this organ are reassuring but caution must still be exercised based on our results. Apart from kidney, thyroid and stomach, only breast cancer risk has been suggested to be increased by one study (Metso et al., 2007) that is contrary to this meta-analysis and earlier studies. (Goldman et al., 1988, Holm et al., 1991, Hoffman and McConahey, 1983)

Conclusion
The thyroid, kidney, and stomach are the only three organs that remain under question in terms of increased cancer risk and need further investigation. While there is no demonstrable increased burden of risk overall after 131I administration, the risks of thyroid, kidney and stomach cancer need to be kept in mind when individualizing therapy. For example, it may be prudent to consider limiting use of ablative 131I to patients without risk factors for the cancers in question. In the case of the thyroid, we could limit ablative use to diffuse toxic goitres or alternatively make efforts to follow-up stringently if administered for treatment of nodular disease. In addition, persons with a history of atrophic gastritis, intestinal metaplasia or dysplasia, gastric ulcers as well as a genetic predisposition to gastric cancer might also best be excluded. In the same way, subjects with acquired or genetic cystic diseases of the kidney, chronic hepatitis C infection, analgesic abuse, or who have received cytotoxic chemotherapy in childhood might also best avoid therapeutic 131I. Fortunately, diagnostic 131I has now been replaced by 99mTc-pertechnetate, so this is no longer of concern.

**Supplementary data**

This is available online

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**Funding**

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References


2929 records retrieved after duplicates removed

2929 record abstracts were screened

2905 records were excluded:
Not relevant or were: case series, case reports, editorials, letters, reviews, errata, animal studies, and laboratory studies.

24 full text articles accessed for eligibility

17 records were excluded:
- Not 131-I therapy or other interventions eg. Surgery or thyroxine therapy or radiation therapy (N = 3)
- No effect sizes (RR or SIR) or no information on precision of the estimate (N = 8).
- Studies not used because of overlapping datasets (N = 6)

7 studies used in the quantitative synthesis

**Figure 1** Flow diagram of the literature search for the meta-analysis
a) Including Franklyn, 1999 (Franklyn et al., 1999)

Figure 2a and 2b: The meta-analysis forest plot depicting the overall burden of cancer risk from 131I on eight major groups of organs (QE model) (a) including Franklyn, 1999 (Franklyn et al., 1999) and (b) excluding Franklyn, 1999 (Franklyn et al., 1999)
<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exposed to 131I</th>
<th>Number of exposed subjects in final cohort</th>
<th>Exposed group</th>
<th>Comparison group</th>
<th>Activities of 131I used (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hoffman 1982</td>
<td>Therapeutic</td>
<td>1005</td>
<td>Hyperthyroid women treated with 131I at Mayo clinic from 01/01/1946 to 31/12/1964</td>
<td>Hyperthyroid women assigned to surgical treatment in Mayo clinic from 01/01/1946 to 31/12/1964</td>
<td>392.2 MBq (equivalent to 10.6 mCi)</td>
</tr>
<tr>
<td>2 Goldman 1988</td>
<td>Therapeutic</td>
<td>607 (approximately equal numbers of women were administered &lt;240 MBq, 240-369 MBq and &gt;= 370 MBq)</td>
<td>Hyperthyroid women treated with 131I at Massachusetts General Hospital Thyroid Unit from 01/01/1946 to 31/12/1964</td>
<td>Cause- age- calendar year- time- sex - matched cancer incidence data in Connecticut from 01/01/1946 to 31/12/1964</td>
<td>NA</td>
</tr>
<tr>
<td>3 Holm 1991</td>
<td>Therapeutic</td>
<td>10207</td>
<td>Hyperthyroid patients treated with 131I in seven Swedish hospitals from 1950 to 1975</td>
<td>Age- sex- region of residence- calendar year- matched cancer incidence data in Sweden from 1958 to 1985</td>
<td>506 MBq</td>
</tr>
<tr>
<td>4 Franklyn 1999</td>
<td>Therapeutic</td>
<td>7417</td>
<td>Hyperthyroid patients treated with 131I in the West Midlands region of the UK from 1950 to 1991</td>
<td>Age- sex- calendar year- matched cancer incidence data in England and Wales from 1950 to 1991</td>
<td>308 MBq (SD= 232 MBq)</td>
</tr>
<tr>
<td>5 Hahn 2001</td>
<td>Diagnostic</td>
<td>789</td>
<td>Children examined for suspected thyroid disease with 131I in 10 German hospitals from 1989 to 1997</td>
<td>Children examined for suspected thyroid disease with other methods than using 131I in 10 German hospitals from 1989 to 1997</td>
<td>0.9 MBq (interquartile range 0.4-1.5; median thyroid absorbed dose 1 Gy)</td>
</tr>
<tr>
<td>6 Dickman 2003</td>
<td>Diagnostic</td>
<td>24010</td>
<td>Patients examined with 131I in seven Swedish hospitals from 1952 to 1969</td>
<td>Age- sex- region of residence- calendar year- matched cancer incidence data in Sweden from</td>
<td>1.6 MBq (mean thyroid absorbed dose 0.94 Gy)</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Therapeutic</td>
<td>Treatment</td>
<td>Matched Group</td>
<td>Activity</td>
</tr>
<tr>
<td>------</td>
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<td>-------------</td>
<td>-----------</td>
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<td>----------</td>
</tr>
<tr>
<td>1958 to 1969</td>
<td>7 Metso 2007</td>
<td>Therapeutic 1302</td>
<td>Hyperthyroid patients treated with 131I in Tampere University Hospital, Finland from 01/1965 to 06/2002</td>
<td>Age- and sex- matched group from the Population Register Centre of Finland</td>
<td>305 MBq</td>
</tr>
</tbody>
</table>

- **a**: Number of patients who were exposed to 131I only
- **b**: The median 131I activity administered.
- **c**: Number of 131I-exposed patients who did not report previous XRT to the neck and were not referred for suspicion of a thyroid tumour.
- **d**: Mean activity administered to patients who did not report previous XRT to the neck region and were not referred for suspicion of a thyroid tumour.
Table 2: Subgroup analysis by duration of follow-up, administered 131I activity, absorbed
dose or age at exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cancer (observed cases in group 1 vs. group 2)</th>
<th>SIR1</th>
<th>SIR2</th>
<th>Ratio of SIR’s</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration of follow-up</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Goldman 1988</td>
<td>All cancer (16 vs. 47) ≥30 years</td>
<td>1.33</td>
<td>0.67</td>
<td>P 2.22</td>
<td>0.67 - 2.22</td>
</tr>
<tr>
<td></td>
<td>Breast (5 vs. 14) &lt;10 years</td>
<td>1.50</td>
<td>0.29</td>
<td>P 3.59</td>
<td>0.29 - 3.59</td>
</tr>
<tr>
<td></td>
<td>Pancreas (6 vs. 3) 20-29 years</td>
<td>1.88</td>
<td>0.53</td>
<td>P 36.14</td>
<td>0.53 - 36.14</td>
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<tr>
<td>Holm 1991</td>
<td>All cancer</td>
<td>0.98</td>
<td>0.85</td>
<td>P 1.14</td>
<td>0.85 - 1.14</td>
</tr>
<tr>
<td></td>
<td>Female breast</td>
<td>0.88</td>
<td>0.63</td>
<td>P 1.24</td>
<td>0.63 - 1.24</td>
</tr>
<tr>
<td></td>
<td>Pancreas (16 vs. 6)</td>
<td>1.59</td>
<td>0.70</td>
<td>P 2.29</td>
<td>0.70 - 2.29</td>
</tr>
<tr>
<td></td>
<td>Leukaemia (12 vs. 8)</td>
<td>1.04</td>
<td>0.44</td>
<td>P 2.36</td>
<td>0.44 - 2.36</td>
</tr>
<tr>
<td></td>
<td>Thyroid (4 vs. 4)</td>
<td>0.86</td>
<td>0.16</td>
<td>P 4.77</td>
<td>0.16 - 4.77</td>
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<tr>
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<td>Parathyroid (11 vs. 8)</td>
<td>0.64</td>
<td>0.26</td>
<td>P 2.54</td>
<td>0.26 - 2.54</td>
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<tr>
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<td>Stomach (35 vs. 16)</td>
<td>1.77</td>
<td>1.03</td>
<td>P 3.53</td>
<td>1.03 - 3.53</td>
</tr>
<tr>
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<td>Liver, gallbladder, bile ducts (9 vs. 17)</td>
<td>0.96</td>
<td>0.45</td>
<td>P 2.09</td>
<td>0.45 - 2.09</td>
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<tr>
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<td>Lung (30 vs. 25)</td>
<td>0.77</td>
<td>0.45</td>
<td>P 1.74</td>
<td>0.45 - 1.74</td>
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<tr>
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<td>Kidney (14 vs. 14)</td>
<td>0.73</td>
<td>0.34</td>
<td>P 2.14</td>
<td>0.34 - 2.14</td>
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<td>Bladder (14 vs. 7)</td>
<td>1.21</td>
<td>0.52</td>
<td>P 2.34</td>
<td>0.52 - 2.34</td>
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<tr>
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<td>Brain (13 vs. 8)</td>
<td>1.40</td>
<td>0.60</td>
<td>P 2.39</td>
<td>0.60 - 2.39</td>
</tr>
<tr>
<td>*Dickman 2003</td>
<td>Thyroid (15 vs. 4) ≥20 years</td>
<td>0.69</td>
<td>0.28</td>
<td>P 2.61</td>
<td>0.28 - 2.61</td>
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<tr>
<td>Goldman 1988</td>
<td>All malignant neoplasms (48 vs. 41)</td>
<td>1.00</td>
<td>0.65</td>
<td>P 1.61</td>
<td>0.65 - 1.61</td>
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<tr>
<td></td>
<td>All Digestive organs (13 vs. 13) ≥370 MBq (10 mCi)</td>
<td>0.82</td>
<td>0.35</td>
<td>P 2.40</td>
<td>0.35 - 2.40</td>
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<tr>
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<td>Pancreas (3 vs. 2)</td>
<td>0.76</td>
<td>0.10</td>
<td>P 7.00</td>
<td>0.10 - 7.00</td>
</tr>
<tr>
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<td>Breast (18 vs. 18)</td>
<td>1.50</td>
<td>0.73</td>
<td>P 2.06</td>
<td>0.73 - 2.06</td>
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<tr>
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<td>Brain (3 vs. 1)</td>
<td>2.50</td>
<td>0.40</td>
<td>P 6.25</td>
<td>0.40 - 6.25</td>
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<tr>
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<td>All other sites (14 vs. 9)</td>
<td>0.78</td>
<td>0.36</td>
<td>P 2.14</td>
<td>0.36 - 2.14</td>
</tr>
<tr>
<td>*Dickman 2003</td>
<td>Thyroid (16 vs. 5) &gt;1.00 Gy ≤0.25 Gy</td>
<td>2.82</td>
<td>1.22</td>
<td>P 14.89</td>
<td>1.22 - 14.89</td>
</tr>
<tr>
<td>*Dickman 2003</td>
<td>Thyroid (2 vs. 11) ≤20 years &gt;50 years</td>
<td>1.02</td>
<td>0.00</td>
<td>P 3.02</td>
<td>0.00 - 3.02</td>
</tr>
<tr>
<td>*Dickman 2003</td>
<td>Thyroid (23 vs. 11) 20-50 years</td>
<td>1.06</td>
<td>0.44</td>
<td>P 2.40</td>
<td>0.44 - 2.40</td>
</tr>
</tbody>
</table>

*Diagnostic absorbed dose**

|                     | Thyroid (16 vs. 5) >1.00 Gy ≤0.25 Gy                   | 2.82 | 1.22 | P 14.89        | 1.22 - 14.89 |

|                     | Thyroid (2 vs. 11) ≤20 years >50 years                 | 1.02 | 0.00 | P 3.02         | 0.00 - 3.02  |

|                     | Thyroid (23 vs. 11) 20-50 years                        | 1.06 | 0.44 | P 2.40         | 0.44 - 2.40  |
2003 (Dickman et al., 2003)

*: Calculated from patients who did not report previous XRT to the neck region and were not referred for suspicion of a thyroid tumor

**The quality factor for all radiations emitted by 131I is assumed to be unity and thus doses in Gy are equivalent to doses in Sv