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

Trinh Trung Hieu1,2, Anthony W Russell3,4, Ross Cuneo3, Justin Clark5, Tomas Kron6, Per Hall7 and Suhail A R Doi1,3

1School of Population Health, University of Queensland, Brisbane, Queensland, Australia
2Department of Clinical Pharmacy, Hanoi University of Pharmacy, Hanoi, Vietnam
3Department of Endocrinology, Princess Alexandra Hospital, Brisbane, Queensland, Australia
4School of Medicine and 5Herston Health Sciences Library, University of Queensland, Brisbane, Queensland, Australia
6Physical Sciences Department, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
7Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

(Correspondence should be addressed to S A R Doi at School of Population Health, University of Queensland; Email: sardoi@gmx.net)

Abstract

Radioiodine-131 (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 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 using 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 which 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in thyroid cancer risk following diagnostic 131I use should no longer be of concern given that it has effectively been replaced by the use of 99mTc-pertechnetate.

Endocrine-Related Cancer (2012) 19 645–655

Introduction

Among 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 (Chapman & Evans 1946, Hertz & Roberts 1946), it is likely that millions of patients with benign thyroid disease have been administered therapeutic or diagnostic activities of 131I. The ease of its administration (Ross 2011), lack of significant adverse effects (Read et al. 2004) and low cost (Ross 2011) have prompted such widespread use even though there still remains some uncertainty in terms of its carcinogenic potential (Glinoer et al. 1987, Solomon et al. 1990, Tominaga et al. 1997, Walsh 2000, 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 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 exposure to $^{131}$I are much less given that the thyroid concentrates most of the radioiodine, and doses to most organs are very small (0.04–0.14 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) have investigated the relationship between cancer risk following therapeutic use of $^{131}$I in benign thyroid disease provide 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 on increased breast (Metso et al. 2007), kidney (Holm et al. 1991) and thyroid (Hoffman et al. 1982, Franklyn et al. 1999) cancer risks are contradicted by other reports on 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 (Holm et al. 1991, Metso et al. 2007). A recent overview of this topic by Verburg et al. (2011) suggests that the evidence is not conclusive in favour of increased risk. However, as 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 $^{131}$I, long periods of follow-up and a large population is required which could be addressed by meta-analysis.

**Materials and methods**

**Data sources and eligibility criteria**

The medical literature, till September 2011, was searched for articles reporting on the diagnostic or therapeutic use of $^{131}$I in benign thyroid diseases and the development of cancer. The references of selected articles were cross-checked for further studies and other language publications were translated where deemed necessary. Details of the search strategy and databases searched are in Supplementary Materials and methods 1, see section on supplementary data given at the end of this article. Inclusion was limited to human studies with exclusions made for $^{131}$I 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 & Thalib (2008) (see Supplementary Materials and methods 2, see section on supplementary data given at the end of this article). The maximum score was ten points and quality was assessed by two independent reviewers. Any discrepancies were addressed by consensus.

**Statistical analysis**

The primary outcome was the relative risk (RR) or the standardised incidence ratio (SIR) for those exposed to radioiodine compared with those not exposed or a standardised 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 standardised population. The RR was defined as the risk of developing a cancer within the follow-up time compared with a control group. SIR and RR were stratified by cancer site. The SIR 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 & 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 the 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 & Gardner 1988; RSIR and 95% CI) in subgroups (defined by duration of follow-up, dose/activity of $^{131}$I and age at the time of exposure; see Supplementary Materials and methods 3, see section on supplementary data given at
the end of this article). To check for publication bias, funnel plot asymmetry could not be used as we had 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 texts of 24 studies were retrieved (Fig. 1). Seventeen of these were then excluded because they were not found to address $^{131}$I use ($n = 3$; Berlin & 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 ($n = 7$; Pochin 1960, Dobyns et al. 1974, Freitas et al. 1979, Spencer et al. 1983, Ozaki et al. 1994, Angusti et al. 2000, Listewnik et al. 2010) or had overlapping datasets ($n = 6$; Saenger et al. 1968, Holm et al. 1980, 1988, Hall & Holm 1995a,b, Hall et al. 1996). Seven studies were finally selected for this meta-analysis (Hoffman et al. 1982, Goldman et al. 1988, Holm et al. 1991, Franklyn et al. 1999, Metso et al. 2007).

**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, Holm et al. 1991, Franklyn et al. 1999, Metso et al. 2007) and two diagnostic studies (Hahn et al. 2001, Dickman et al. 2003). There were 22 029 exposed subjects in the therapeutic cohorts and 24 799 in the diagnostic cohorts (see Table 1). Although the data source in the study by Dickman et al. (2003) overlapped with the study by Holm et al. (1991), the focus was diagnostic in the former study; and patients with therapeutic use of $^{131}$I were excluded. The population considered 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 (Hoffman et al. 1982, Hahn et al. 2001, Metso et al. 2007), while the other four studies reported 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 Table 1, see section on supplementary data given at the end of this article 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) or medical records

---

**Figure 1** Flow diagram of the literature search for the meta-analysis.
from the Cooperative Thyrotoxicosis Therapy Follow-up Study.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exposed to $^{131}$I</th>
<th>Number of exposed subjects in final cohort</th>
<th>Exposed group</th>
<th>Comparison group</th>
<th>Activities of $^{131}$I used (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et al. (1982)</td>
<td>Therapeutic</td>
<td>1005</td>
<td>Hyperthyroid women treated with $^{131}$I 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>Goldman et al. (1988)</td>
<td>Therapeutic</td>
<td>607&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hyperthyroid women treated with $^{131}$I 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 (approximately equal numbers of women were administered &lt;240, 240–369 and ≥370 MBq)</td>
</tr>
<tr>
<td>Holm et al. (1991)</td>
<td>Therapeutic</td>
<td>10 207</td>
<td>Hyperthyroid patients treated with $^{131}$I 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>Franklyn et al. (1999)</td>
<td>Therapeutic</td>
<td>7417</td>
<td>Hyperthyroid patients treated with $^{131}$I 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 (s.d. = 232 MBq)</td>
</tr>
<tr>
<td>Hahn et al. (2001)</td>
<td>Diagnostic</td>
<td>789</td>
<td>Children examined for suspected thyroid disease with $^{131}$I in 10 German hospitals from 1989 to 1997</td>
<td>Children examined for suspected thyroid disease with other methods than using $^{131}$I in ten German hospitals from 1989 to 1997</td>
<td>0.9 MBq&lt;sup&gt;b&lt;/sup&gt; (interquartile range 0.4–1.5; median thyroid-absorbed dose 1 Gy)</td>
</tr>
<tr>
<td>Dickman et al. (2003)</td>
<td>Diagnostic</td>
<td>24 010&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Patients examined with $^{131}$I in seven Swedish hospitals from 1952 to 1969</td>
<td>Age- sex- region of residence- calendar year-matched cancer incidence data in Sweden from 1958 to 1969</td>
<td>1.6 MBq&lt;sup&gt;d&lt;/sup&gt; (mean thyroid-absorbed dose 0.94 Gy)</td>
</tr>
<tr>
<td>Metso et al. (2007)</td>
<td>Therapeutic</td>
<td>2793</td>
<td>Hyperthyroid patients treated with $^{131}$I 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>

<sup>a</sup>Number of patients who were exposed to $^{131}$I only.

<sup>b</sup>The median $^{131}$I activity administered.

<sup>c</sup>Number of $^{131}$I-exposed patients who did not report previous radiotherapy to the neck and were not referred for suspicion of a thyroid tumour.

<sup>d</sup>Mean activity administered to patients who did not report previous radiotherapy to the neck region and were not referred for suspicion of a thyroid tumour.

Quantitative synthesis of data (therapeutic use only)

Overall cancer risk

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

Organ groups that concentrate $^{131}$I

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 study by Franklyn et al. (1999) after which risk increased (RR 1.17, 95% CI: 1.06–1.30). The latter was mainly because the study by Franklyn et al. (1999) had protective estimates for digestive organs and peritoneum; lip, oral cavity and pharynx; and bone, connective tissues, skin and breast, although none were significant and were most likely random changes (see Supplementary Figure 2, see section on supplementary data given at the end of this article).

Individual organ groups

Seven organ groups (Fig. 2) from five papers did not demonstrate an increase in cancer risk (Supplementary Figure 1, see section on supplementary data given at the end of this article). Digestive and respiratory organs were, however, sensitive to exclusion of the study by Franklyn et al. (1999), resulting in borderline significance in favour of increased risk (lower confidence limit of 1.01–1.03, Fig. 2b). Conventional weighting methods suggest a slight difference in direction of the pooled estimate for digestive organs and peritoneum; lip, oral cavity and pharynx; and bone, connective tissues, skin and breast, although none were significant and were most likely random changes (see Supplementary Figure 2, see section on supplementary data given at the end of this article).

Individual organs

Nine individual organs (salivary glands, breast, kidney, bladder, lymphoma, leukaemia, pancreas, stomach and thyroid) reported by five studies reveal a higher risk of only kidney and thyroid cancers, while stomach cancer demonstrated a non-significant trend (Supplementary...
perform a stratified analysis. Meta-analysis because there was not enough data to 2003; Table 2). This was done in lieu of a subgroup Dickman et al (1999). Metso (95% CI: 0.1–5.1) in childhood exposure vs 0.91 (95% CI: 0.91–2.75). The RR (or SIR) for thyroid cancer was 0.9 undertook on adults (only 7% were below the age of 20 years). The RR (or SIR) for thyroid cancer was 0.9 (95% CI: 0.1–5.1) in childhood exposure vs 0.91 (95% CI: 0.64–1.26) in adult exposure (excluding subjects with prior radiation therapy or referred for suspicion of a tumour). 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: 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 (Kennedy & Fish 1959, McCormack & Sheline 1963, Bundi et al. 1977, Munoz et al. 1978, Spencer et al. 1983) 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 radiiodine (salivary glands, digestive tract and urinary tract) did not demonstrate an increased risk of cancer. Individual studies on overall (Holm et al. 1991, Metso et al. 2007) or CG (Hoffman et al. 1982) risks 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 the 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 (de Vathaire et al. 1988, Tucker et al. 1991), 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,
The two studies that demonstrate an increase in the risk of thyroid cancer (Hoffman et al. 1982, Franklyn et al. 1999) differ from the other studies. The study by Hoffman et al. (1982) reports an RR 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 study by Franklyn et al. (1999) data on cancer incidence (for patients and controls) were drawn from different sources, so bias was likely. 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 study by 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 as thyroid cancer is far more common in those with nodular thyroid disease (as compared with Graves’; Angusti et al. 2000). 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 who did not presumably have nodular

---

### 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>Types 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><strong>Duration of follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldman et al. (1988)</td>
<td>All cancer (16 vs 47)</td>
<td>≥ 30 years</td>
<td>&lt;10 years</td>
<td>1.33</td>
<td>0.67–2.22</td>
</tr>
<tr>
<td></td>
<td>Breast (5 vs 14)</td>
<td></td>
<td></td>
<td>1.50</td>
<td>0.29–3.59</td>
</tr>
<tr>
<td></td>
<td>Pancreas (6 vs 3)</td>
<td>20–29 years</td>
<td>1.88</td>
<td>0.53–36.14</td>
<td></td>
</tr>
<tr>
<td>Holm et al. (1991)</td>
<td>All cancer</td>
<td>≥ 15 years</td>
<td>1–4 years</td>
<td>0.98</td>
<td>0.85–1.14</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td></td>
<td></td>
<td>0.88</td>
<td>0.63–1.24</td>
</tr>
<tr>
<td></td>
<td>Pancreas (16 vs 6)</td>
<td></td>
<td></td>
<td>1.59</td>
<td>0.70–6.29</td>
</tr>
<tr>
<td></td>
<td>Leukaemia (12 vs 8)</td>
<td></td>
<td></td>
<td>1.04</td>
<td>0.44–3.06</td>
</tr>
<tr>
<td></td>
<td>Thyroid (4 vs 4)</td>
<td></td>
<td></td>
<td>0.86</td>
<td>0.16–4.77</td>
</tr>
<tr>
<td></td>
<td>Parathyroid (11 vs 8)</td>
<td></td>
<td></td>
<td>0.64</td>
<td>0.26–1.86</td>
</tr>
<tr>
<td></td>
<td>Stomach (35 vs 16)</td>
<td></td>
<td></td>
<td>1.77</td>
<td>1.03–3.53</td>
</tr>
<tr>
<td></td>
<td>Liver, gallbladder and bile ducts (9 vs 17)</td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.45–2.60</td>
</tr>
<tr>
<td></td>
<td>Lung (30 vs 25)</td>
<td></td>
<td></td>
<td>0.77</td>
<td>0.45–1.34</td>
</tr>
<tr>
<td></td>
<td>Kidney (14 vs 14)</td>
<td></td>
<td></td>
<td>0.73</td>
<td>0.34–1.60</td>
</tr>
<tr>
<td></td>
<td>Bladder (14 vs 7)</td>
<td></td>
<td></td>
<td>1.21</td>
<td>0.52–3.98</td>
</tr>
<tr>
<td></td>
<td>Brain (13 vs 8)</td>
<td></td>
<td></td>
<td>1.40</td>
<td>0.60–4.10</td>
</tr>
<tr>
<td>Dickman et al. (2003)a</td>
<td>Thyroid (15 vs 4)</td>
<td>≥ 20 years</td>
<td>2–5 years</td>
<td>0.69</td>
<td>0.28–6.61</td>
</tr>
<tr>
<td>Therapeutic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldman et al. (1988)</td>
<td>All malignant neoplasms (48 vs 41)</td>
<td>≥ 370 MBq (10 mCi)</td>
<td>No 131I</td>
<td>1.00</td>
<td>0.65–1.61</td>
</tr>
<tr>
<td></td>
<td>All digestive organs (13 vs 13)</td>
<td></td>
<td></td>
<td>0.82</td>
<td>0.35–2.40</td>
</tr>
<tr>
<td></td>
<td>Pancreas (3 vs 2)</td>
<td></td>
<td></td>
<td>0.76</td>
<td>0.10–50.07</td>
</tr>
<tr>
<td></td>
<td>Breast (18 vs 18)</td>
<td></td>
<td></td>
<td>1.50</td>
<td>0.73–3.81</td>
</tr>
<tr>
<td></td>
<td>Brain (3 vs 1)</td>
<td></td>
<td></td>
<td>2.50</td>
<td>0.40–82.50</td>
</tr>
<tr>
<td></td>
<td>All other sites (14 vs 9)</td>
<td></td>
<td></td>
<td>0.78</td>
<td>0.36–1.74</td>
</tr>
<tr>
<td>Diagnostic-absorbed doseb</td>
<td>Thyroid (16 vs 5)</td>
<td>&gt;1.00 Gy</td>
<td>≤0.25 Gy</td>
<td>2.82</td>
<td>1.22–14.89</td>
</tr>
<tr>
<td>Age at exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dickman et al. (2003)a</td>
<td>Thyroid (2 vs 11)</td>
<td>≤20 years</td>
<td>&gt;50 years</td>
<td>1.02</td>
<td>0.00–3.02</td>
</tr>
<tr>
<td></td>
<td>Thyroid (23 vs 11)</td>
<td>20–50 years</td>
<td></td>
<td>1.06</td>
<td>0.44–2.40</td>
</tr>
</tbody>
</table>

---

*aCalculated from patients who did not report previous XRT to the neck region and were not referred for suspicion of a thyroid tumour.

bThe quality factor for all radiations emitted by 131I is assumed to be unity and thus doses in Gray are equivalent to doses in Sievert.


The two studies that demonstrate an increase in the risk of thyroid cancer (Hoffman et al. 1982, Franklyn et al. 1999) differ from the other studies. The study by Hoffman et al. (1982) reports an RR 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 study by Franklyn et al. (1999) data on cancer incidence (for patients and controls) were drawn from different sources, so bias was likely. 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 study by 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 as thyroid cancer is far more common in those with nodular thyroid disease (as compared with Graves’; Angusti et al. 2000). 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 who did not presumably have nodular
uptake, a thyroid scan with 1.85–7.4 MBq$^{131}$I orally has been estimated that for an adult, assuming a 15% 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$^{131}$I orally exposes the thyroid to 388–1554 mGy (SNM 1999) and the study by Dickman et al. (2003) demonstrated an increased SIR when the dose was > 1000 mGy as compared with < 250 mGy. This might be of concern given that this was an absorbed dose to a non-ablated thyroid gland. Nowadays, however, it is much more common to use 75–370 MBq 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 5–23 mGy. (SNM 1999). While there is little evidence to suggest that the use of diagnostic$^{131}$I 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 100 mGy (Kloos 2011), and after repeated X-ray examinations, an excess of cancer is reported only for cumulative doses > 500 mGy (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$^{131}$I therapy (Suit et al. 2007) and doses to other organs (apart from the stomach) parallel doses received from common medical imaging procedures, ranging up to 20 mGy (highest for chest/abdominal CT and coronary angiography).

The highest non-thyroidal exposure is reported to be the stomach at about 0.41 mGy/MBq (Zanzonico 2000), the total dose averaging 250 mGy (Edmonds & Smith 1986, Huysmans et al. 1996). Within the gastrointestinal system, the stomach is most exposed, since ingested$^{131}$I 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 et al. (1999)) concur in terms of increasing trend for stomach cancer (Hoffman et al. 1982, Holm et al. 1991, Metso et al. 2007) even though the meta-analysis of neither the digestive tract cancer on the whole nor the stomach cancer revealed increased risk. The strongest effect was with the study by Metso et al. (2007) (stomach cancer had 30 cases in the exposed group and an RR 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 (of the regression line fitted through the risk values as a function of dose) for the stomach is significantly positive (Suit et al. 2007) and it might therefore be prudent to consider caution especially 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 (Hoffman et al. 1982, Holm et al. 1991, Franklyn et al. 1999), though two studies (Holm et al. 1991, Metso et al. 2007) 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 was not different from unity for kidney cancer. However, there were 90 cases of kidney cancer reported in three studies (Hoffman et al. 1982, Holm et al. 1991, Metso et al. 2007) and this raises concern. Fortunately, data from patients treated with radiation suggest that the RR (radiotherapy to general population) as a function of dose up to 15 Gy 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 risk of breast cancer has been suggested to be increased by one study (Metso et al. 2007) which is contrary to this meta-analysis and earlier studies (Hoffman & McConahey 1983, Goldman et al. 1988, Holm et al. 1991).

**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 $^{131}$I administration, the risks of thyroid, kidney and stomach cancers need to be kept in mind when individualising therapy. For example, it may be prudent to consider limiting use of ablative $^{131}$I 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 and 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 $^{131}$I. Fortunately, diagnostic $^{131}$I has now been replaced by 99mTc-pertechnetate, so this is no longer of concern.

**Supplementary data**

This is linked to the online version of the paper at [http://dx.doi.org/10.1530/ERC-12-0176](http://dx.doi.org/10.1530/ERC-12-0176).

**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**

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**References**


Dobyns BM, Sheline GE & Workman JB 1974 Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy. Follow up study. *Journal of Clinical Endocrinology and Metabolism* 38 976–998. ([doi:10.1210/jcem-38-6-976](https://doi.org/10.1210/jcem-38-6-976))

Doi SA & Thalib L 2008 A quality-effects model for meta-analysis. *Epidemiology* 19 94–100. ([doi:1097/EDE.0b013e31815c24e7](https://doi.org/1097/EDE.0b013e31815c24e7))


Hertz S & Roberts A 1946 Radioactive iodine in the study of thyroid physiology; the use of radioactive iodine therapy in hyperthyroidism. Journal of the American Medical Association 131 81–86. (doi:10.1001/jama.1946.02870190005002)


Ross DS 2011 Radioiodine therapy for hyperthyroidism. 
(doi:10.1056/NEJMc1007101)

Saenger EL, Thoma GE & Tompkins EA 1968 Incidence 
of leukemia following treatment of hyperthyroidism. 
*Journal of the American Medical Association* **205** 

SNM 1999 Society of Nuclear Medicine Procedure Guideline 
for Thyroid Scintigraphy (online). Society of Nuclear 
docs/pg_ch05_0403.pdf (accessed 17/04/2012).

Solomon B, Glinoer D, Lagasse R & Wartofsky L 1990 
Current trends in the management of Graves’ disease. 
*Journal of Clinical Endocrinology and Metabolism* **70** 
1518–1524. (doi:10.1210/jcem-70-6-1518)

Spencer RP, Chapman CN & Rao H 1983 Thyroid carcinoma 
after radioiodide therapy for hyperthyroidism. Analysis 
based on age, latency, and administered dose of I-131. 
00003072-198305000-00007)

Suit H, Goldberg S, Niemierko A, Ancukiewicz M, Hall E, 
Goitein M, Wong W & Paganetti H 2007 Secondary 
carcinogenesis in patients treated with radiation: a review 
of data on radiation-induced cancers in human, non-
human primate, canine and rodent subjects. *Radiation 
Research* **167** 12–42. (doi:10.1667/RR0527.1)

Takkouche B, Cadarso-Suarez C & Spiegelman D 1999 
Evaluation of old and new tests of heterogeneity in 
epidemiologic meta-analysis. *American Journal of 
aje.a009981)

Tominaga T, Yokoyama N, Nagataki S, Cho BY, Koh CS, 
Chen JL & Shi Y 1997 International differences in 
approaches to 131I therapy for Graves’ disease: case 
selection and restrictions recommended to patients 
(doi:10.1089/thy.1997.7.217)

Tucker MA, Jones PH, Boice JD Jr, Robison LL, Stone BJ, 
Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE 
et al. 1991 Therapeutic radiation at a young age is linked 
to secondary thyroid cancer. The late effects study group. 
*Cancer Research* **51** 2885–2888.

Vaiserman AM 2010 Radiation hormesis: historical 
perspective and implications for low-dose cancer 
risk assessment. *Dose–response: a Publication of 

de Vathaire F, Francois P, Schweisguth O, Oberlin O & 
Le Monique G 1988 Irradiated neuroblastoma in child-
hood as potential risk factor for subsequent thyroid tumour. 

Verburg FA, Luster M, Lassmann M & Reiners C 2011 (131)I 
therapy in patients with benign thyroid disease does not 
conclusively lead to a higher risk of subsequent malign-

*Australian and New Zealand Journal of Medicine* **30** 

Zanzonico PB 2000 Age-dependent thyroid absorbed doses 
for radiobiologically significant radioisotopes of iodine. 
*Health Physics* **78** 60–67. (doi:10.1097/00004032- 
200001000-00010)

Received in final form 6 July 2012
Accepted 31 July 2012
Made available online as an Accepted Preprint 
31 July 2012