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

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in thyroid cancer risk following diagnostic ¹³¹I use should no longer be of concern given that it has effectively been replaced by the use of 99mTc-pertechnetate.

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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

(Glinoe *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) that 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 τ^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, Mellemegaard *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, Hahn *et al.* 2001, Dickman *et al.* 2003, 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.

Table 1 Characteristics of the included studies

Study	Reason for exposed to ¹³¹ I	Number of exposed subjects in final cohort	Exposed group	Comparison group	Activities of ¹³¹ I used (mean)
Hoffman <i>et al.</i> (1982)	Therapeutic	1005	Hyperthyroid women treated with ¹³¹ I at Mayo clinic from 01/01/1946 to 31/12/1964	Hyperthyroid women assigned to surgical treatment in Mayo clinic from 01/01/1946 to 31/12/1964	392.2 MBq (equivalent to 10.6 mCi)
Goldman <i>et al.</i> (1988)	Therapeutic	607 ^a	Hyperthyroid women treated with ¹³¹ I at Massachusetts General Hospital Thyroid Unit from 01/01/1946 to 31/12/1964	Cause- age- calendar year- time- sex-matched cancer incidence data in Connecticut from 01/01/1946 to 31/12/1964	NA (approximately equal numbers of women were administered <240, 240–369 and ≥370 MBq)
Holm <i>et al.</i> (1991)	Therapeutic	10 207	Hyperthyroid patients treated with ¹³¹ I in seven Swedish hospitals from 1950 to 1975	Age- sex- region of residence- calendar year-matched cancer incidence data in Sweden from 1958 to 1985	506 MBq
Franklyn <i>et al.</i> (1999)	Therapeutic	7417	Hyperthyroid patients treated with ¹³¹ I in the West Midlands region of the UK from 1950 to 1991	Age- sex- calendar year-matched cancer incidence data in England and Wales from 1950 to 1991	308 MBq (s.d. =232 MBq)
Hahn <i>et al.</i> (2001)	Diagnostic	789	Children examined for suspected thyroid disease with ¹³¹ I in 10 German hospitals from 1989 to 1997	Children examined for suspected thyroid disease with other methods than using ¹³¹ I in ten German hospitals from 1989 to 1997	0.9 MBq ^b (interquartile range 0.4–1.5; median thyroid-absorbed dose 1 Gy)
Dickman <i>et al.</i> (2003)	Diagnostic	24 010 ^c	Patients examined with ¹³¹ I in seven Swedish hospitals from 1952 to 1969	Age- sex- region of residence- calendar year-matched cancer incidence data in Sweden from 1958 to 1969	1.6 MBq ^d (mean thyroid-absorbed dose 0.94 Gy)
Metso <i>et al.</i> (2007)	Therapeutic	2793	Hyperthyroid patients treated with ¹³¹ I in Tampere University Hospital, Finland from 01/1965 to 06/2002	Age- and sex-matched group from the Population Register Centre of Finland	305 MBq

^aNumber of patients who were exposed to ¹³¹I only.

^bThe median ¹³¹I activity administered.

^cNumber of ¹³¹I-exposed patients who did not report previous radiotherapy to the neck and were not referred for suspicion of a thyroid tumour.

^dMean activity administered to patients who did not report previous radiotherapy to the neck region and were not referred for suspicion of a thyroid tumour.

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).

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

Figure 2 The meta-analysis forest plot depicting the overall burden of cancer risk from ^{131}I on eight major groups of organs (QE model; a) including Franklyn *et al.* (1999) and (b) excluding Franklyn *et al.* (1999).

(RR 1.06, 95% CI: 0.94–1.19; Fig. 2a). Results were sensitive to exclusion of the study by Franklyn *et al.* (1999), exclusion of 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 and genitourinary organs. Similar results were obtained with conventional weighting (RR 1.06, 95% CI: 0.98–1.13) compared with RR 1.12 (95% CI: 1.04–1.21) after removal of the study by Franklyn *et al.* (1999).

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 groups 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

Figure 1, see section on [supplementary data](#) given at the end of this article).

The kidney cancer RR was 1.70 (95% CI: 1.15–2.51) from data in three studies. Exclusion of the study by [Metso *et al.* \(2007\)](#) decreases the significance of the kidney cancer result and puts most of the weight on the study by [Holm *et al.* \(1991\)](#).

The thyroid cancer risk (RR: 1.99, 95% CI: 1.22–3.26) was mitigated by excluding the study by [Franklyn *et al.* \(1999\)](#), resulting in an RR of 1.58 (95% CI: 0.91–2.75). These studies had less than ten observed cases of thyroid cancer ([Hoffman *et al.* 1982](#), [Franklyn *et al.* 1999](#), [Metso *et al.* 2007](#)) and the study by [Holm *et al.* \(1991\)](#) with 18 observed cases did not demonstrate increased risk. Conventional weighting methods concurred with these results (see [Supplementary Figure 2](#), see section on [supplementary data](#) given at the end of this article).

Finally, the only two studies, [Hahn *et al.* \(2001\)](#) and [Dickman *et al.* \(2003\)](#), on diagnostic ^{131}I 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 on children only ([Hahn *et al.* 2001](#)) while the other ([Dickman *et al.* 2003](#)) was predominantly undertaken 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: 3.96–13.40) referral for a thyroid tumour.

Stratification by time since exposure, age at exposure, absorbed dose and administered activity of ^{131}I

To examine the effect of time since exposure, age at exposure and dose of ^{131}I on cancer risk, we calculated the ratio of the SIRs (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](#); [Table 2](#)). 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 ^{131}I 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 and therapeutic activity administration was 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 > 1 Gy had 2.82 times the SIR compared with patients with an absorbed dose of < 0.25 Gy (ratio of SIRs 2.82, 95% CI: 1.22–14.89), although neither of the stratum-specific SIRs were significant. The therapeutic study ([Goldman *et al.* 1988](#)) reported that > 10 mCi compared with no administration of ^{131}I did not significantly alter SIR estimates.

Finally, there was no trend of increasing SIR of thyroid cancer as age at exposure to ^{131}I 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 ([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 ^{131}I , 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 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 ^{131}I exposure that remain far from the reported dangerous threshold of between 100 and 1000 mGy ([Kloos 2011](#)). This level of exposure is reached, after ^{131}I 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 ^{131}I for treatment of hyperthyroidism ([Dobyns *et al.* 1974](#),

Table 2 Subgroup analysis by duration of follow-up, administered ¹³¹I activity, absorbed dose or age at exposure

Study	Types of cancer (observed cases in group 1 vs group 2)	SIR1	SIR2	Ratio of SIR's	95% CI
Duration of follow-up					
Goldman <i>et al.</i> (1988)	All cancer (16 vs 47)	≥ 30 years	< 10 years	1.33	0.67–2.22
	Breast (5 vs 14)			1.50	0.29–3.59
	Pancreas (6 vs 3)	20–29 years		1.88	0.53–36.14
Holm <i>et al.</i> (1991)	All cancer	≥ 15 years	1–4 years	0.98	0.85–1.14
	Breast			0.88	0.63–1.24
	Pancreas (16 vs 6)			1.59	0.70–6.29
	Leukaemia (12 vs 8)			1.04	0.44–3.06
	Thyroid (4 vs 4)			0.86	0.16–4.77
	Parathyroid (11 vs 8)			0.64	0.26–1.86
	Stomach (35 vs 16)			1.77	1.03–3.53
	Liver, gallbladder and bile ducts (9 vs 17)			0.96	0.45–2.60
	Lung (30 vs 25)			0.77	0.45–1.34
	Kidney (14 vs 14)			0.73	0.34–1.60
	Bladder (14 vs 7)			1.21	0.52–3.98
	Brain (13 vs 8)			1.40	0.60–4.10
	Thyroid (15 vs 4)	≥ 20 years	2–5 years	0.69	0.28–6.61
Dickman <i>et al.</i> (2003) ^a					
Therapeutic activity					
Goldman <i>et al.</i> (1988)	All malignant neoplasms (48 vs 41)	≥ 370 MBq (10 mCi)	No ¹³¹ I	1.00	0.65–1.61
	All digestive organs (13 vs 13)			0.82	0.35–2.40
	Pancreas (3 vs 2)			0.76	0.10–50.07
	Breast (18 vs 18)			1.50	0.73–3.81
	Brain (3 vs 1)			2.50	0.40–82.50
	All other sites (14 vs 9)			0.78	0.36–1.74
Diagnostic-absorbed dose ^b					
Dickman <i>et al.</i> (2003) ^a	Thyroid (16 vs 5)	> 1.00 Gy	≤ 0.25 Gy	2.82	1.22–14.89
Age at exposure					
Dickman <i>et al.</i> (2003) ^a	Thyroid (2 vs 11)	≤ 20 years	> 50 years	1.02	0.00–3.02
Dickman <i>et al.</i> (2003) ^a	Thyroid (23 vs 11)	20–50 years		1.06	0.44–2.40

^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.

Holm *et al.* 1980, 1991, Goldman *et al.* 1988, Angusti *et al.* 2000, Metso *et al.* 2007).

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

disease and who received ^{131}I for Graves' disease, followed-up for 36 years, revealed no cases of thyroid cancer (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 ^{131}I use had no increase in risk demonstrable, and this concurs with several studies of diagnostic ^{131}I use in children or adolescents (Holm *et al.* 1988, Hall *et al.* 1996, Hahn *et al.* 2001, 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 ^{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 $^{99\text{m}}\text{Tc}$ -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 & McConeahey 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 $^{99\text{m}}\text{Tc}$ -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>.

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.

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