Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis
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CRD summary
This review concluded that risk of second primary malignancies in thyroid cancer survivors treated with radioactive iodine was slightly increased compared to survivors not treated with radioactive iodine. This was generally a well-conducted review, but the findings were undermined by the small number of included studies of uncertain methodological quality and so the authors' conclusion should be interpreted with caution.

Authors' objectives
To determine if the risk of second primary malignancies is increased in individuals with thyroid cancer treated with radioactive iodine compared to those not treated with radioactive iodine.

Searching
MEDLINE, MEDLINE In-Process and Other Non-indexed Citations, Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, all Evidence-Based Medicine Reviews (including DARE and Cochrane Central Register of Controlled Trials), EMBASE, CINAHL and HealthStar were searched without language restrictions. Dates ranged from 1966 to September 2008. Included studies were cross-referenced and experts contacted to identify any additional articles of interest.

Study selection
Published English-language cohort studies, cross-sectional studies, cancer registries, administrative datasets, meta-analyses and large case series (at least 50 thyroid carcinoma patients) that compared the risk of second primary malignancy in individuals with thyroid cancer treated with radioactive iodine compared to individuals with thyroid cancer not treated with radioactive iodine were eligible for inclusion. Therapy received included radioisotope or radioisotope with external beam radiotherapy, external beam radiotherapy alone or brachytherapy. Where specified, mean cumulative radioactive iodine activity was 6.0GBq (range 0.2 to 55.5GBq). Second primary malignancies were required to have been diagnosed after an initial diagnosis of thyroid cancer; recurrences of thyroid cancer were not considered second primary malignancies. Eligible studies had to report a relative risk, odds ratio, or hazard ratio (with respective 95% confidence intervals) that compared second primary malignancy risk in thyroid cancer patients treated with radioactive iodine to those not treated with radioactive iodine, or reported the information to calculate these ratios and their 95% confidence intervals (CIs). Included studies were of survivors of papillary or follicular thyroid carcinoma and reported outcomes for either specific second primary malignancies or any second primary malignancy. In the included studies: median or mean age of thyroid cancer diagnosis was just over 40 years of age; stage of thyroid cancer at diagnosis was not reported; and the proportion of individuals who developed one or more second primary malignancies ranged from 7.1% to 8.4%. Median time to development of a second primary malignancy after a thyroid cancer diagnosis was 8.1 years in one study and a mean time of 15 years in the other.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed using: method of data collection; numerical description of the eligible participants excluded from the study and losses to follow-up; and independent confirmation of thyroid cancer and second primary malignancy diagnoses.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Relative risk (RR) and 95% CIs were extracted for various types of second primary malignancies. Where the relative risk was not reported, it was calculated by dividing the standardised incidence ratio of second primary malignancy in individuals with thyroid cancer treated with radioactive iodine compared to those not treated with radioactive iodine.

Two reviewers independently abstracted data, which was reviewed for accuracy by a third reviewer; discrepancies were resolved by consensus between all three reviewers.

**Methods of synthesis**

Studies were combined in a meta-analysis using a fixed-effect model using inverse variance weighting. Summary estimates were reported as relative risks and their associated 95% CIs. Heterogeneity was assessed using $I^2$ test and $T^2$ value.

**Results of the review**

Two studies (n=37,119, range 6,841 to 30,278) were included in the review. Study quality was uncertain: losses to follow-up were reported in one study (20%); it was not clearly reported whether there was any independent confirmation of cancer diagnoses; neither study clearly reported the method of data collection; and there was no clear numerical description of the eligible participants excluded from either study. The median follow-up was 8.6 years in one study and 13 years in the other.

Compared to those not treated with radioactive iodine, the risk of any second primary malignancies was significantly increased in thyroid cancer survivors treated with radioactive iodine using a minimum latency period of two to three years after thyroid cancer diagnosis (RR 1.19, 95% CI 1.04 to 1.36, p=0.01; n=16,502). There was significant heterogeneity for this analysis. Compared to those not treated with radioactive iodine, the risk of leukemia was significantly increased in thyroid cancer survivors treated with radioactive iodine (RR 2.50, 95% CI 1.13 to 5.53, p=0.02). A random-effects analysis confirmed the robustness of the findings.

There was no significantly increased pooled risk of additional cancers associated with prior radioactive iodine treatment (pooled cancers included bladder, breast, central nervous system, colon and rectum, digestive tract, stomach, pancreas, kidney and renal pelvis, lung and melanoma of skin).

**Authors’ conclusions**

The risk of second primary malignancies in thyroid cancer survivors treated with radioactive iodine was slightly increased compared to thyroid cancer survivors not treated with radioactive iodine.

**CRD commentary**

The review question was clear and was supported by specific inclusion criteria. The thorough literature search was restricted to published studies in English; language and publication bias could have been present. Both study selection and data extraction were undertaken by multiple reviewers, which reduced potential for error and bias; it was unclear whether this extended to study quality. Appropriate criteria were used to assess study quality, but there was a lack of clarity in the included studies as to whether the criteria were addressed or not. It appeared that both studies were of poor quality. The studies were combined by meta-analysis and heterogeneity was investigated. Significant heterogeneity was found for the comparison of all second primary malignancies, which suggested that the meta-analysis results for this comparison should be treated with caution. This was generally a well-conducted review, but the findings were undermined by the small number of included studies of uncertain methodological quality and so the authors’ conclusion should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors did not state implications for practice.

Research: The authors stated that further studies with longer follow-up and in additional populations were required, as were an examination of genetic susceptibility for second primary malignancy risk after radioactive iodine treatment. The relationships between dose activity, thyroid cancer disease stage, family history and lifestyle factors with second primary malignancy risk in thyroid cancer survivors should also be addressed.
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