Thyroid

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Long-Term Effects of Radioiodine Treatment on Female Fertility in Survivors of Childhood Differentiated Thyroid Carcinoma

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Abstract

Background. Differentiated thyroid cancer (DTC) during childhood is a rare disease. Its excellent survival rate requires a focus on possible long-term adverse effects. This study aimed to evaluate fertility in female survivors of childhood DTC by assessing various reproductive characteristics combined with anti-Müllerian hormone (AMH) levels (a marker of ovarian reserve).

Methods. Female survivors of childhood DTC, diagnosed at ≤18 years of age between 1970 and 2013 were included. Survivors were excluded when follow-up time was less than 5 years or if they developed other malignancies before or after diagnosis of DTC. Survivors filled out a questionnaire regarding reproductive characteristics (*e.g.* age at menarche and menopause, pregnancies, pregnancy outcomes, need for assisted reproductive therapy). Survivors aged <18 years during evaluation received an altered questionnaire without questions regarding pregnancy and pregnancy outcomes. These data were combined with information from medical records. AMH levels were measured in serum samples and were compared with AMH levels from 420 women not treated for cancer.

Results. Fifty-six survivors with a median age of 31.0 years (interquartile range [IQR] 25.1-39.6 years) were evaluated after a median follow-up of 15.4 years (IQR 8.3-24.7 years). The median cumulative dose of radioactive iodine (131-I) administered was 7.4 GBq (IQR 3.7-13.0 GBq/200.0 mCi, IQR 100.0-350.0 mCi). Twenty-five out of 55 survivors aged 18 years or older during evaluation reported 64 pregnancies, 45 of which resulted in live birth. Of these 55, 10.9% visited a fertility clinic. None of the survivors reported premature menopause. Age at AMH evaluation did not differ between DTC survivors and the comparison group (P = 0.268). Median AMH levels did not differ between DTC survivors and the comparison group (2.0 µg/L [IQR 1.0–3.7 µg/L] vs.1.6 µg/L [IQR 0.6–3.1 µg/L], respectively, P = 0.244). The cumulative dose of 131-I was not associated with AMH levels in DTC survivors (r_s = 0.210, P = 0.130).

Conclusions. Female survivors of DTC who received 131-I treatment during childhood do not appear to have major abnormalities in reproductive characteristics nor in predictors of ovarian failure.

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Introduction

Childhood differentiated thyroid carcinoma (DTC) is rare, with age-adjusted incidences reported between 0.6 and 1.2 per 100,000 per year (1, 2). Up to puberty, the female:male ratio is similar, but after puberty mainly females are diagnosed with the disease (3). In all age groups, a rise in incidence rates of thyroid cancer has been reported (4). Treatment of pediatric DTC most commonly consists of total thyroidectomy with or without central or lateral neck dissection (5). After surgery, radioactive iodine (131-I) is often administered. Depending on the risk classification of the patient a certain intensity of thyrotropin (TSH) suppression is pursued. Although this treatment results in excellent survival rates, up to 99% after 30 years of follow-up (6), DTC treatment, especially therapy with 131-I, calls for examination of possible long-term adverse effects: reproductive characteristics, secondary cancers, salivary dysfunction, bone marrow suppression, and alterations in quality of life (7-12).

Female fertility after treatment with 131-I has been evaluated in survivors of *childhood* and *adult* DTC. Only two studies examined survivors of *childhood* DTC and were limited by small numbers of patients and unclear or ill-defined endpoints (9, 13). Studies in survivors of *adult* DTC found conflicting results regarding the effect of 131-I on female fertility, although permanent impairment of fertility is not common (14-21).

Anti-Müllerian Hormone (AMH) is released by the granulosa cells and is a reflection of the number of antral follicles in the ovaries. Although there is no consensus on the clinical value of AMH, it is a commonly used marker for ovarian reserve in cancer survivors (36), partly because AMH is not influenced by menstrual cycle fluctuations (22, 23). AMH levels in adult DTC patients decrease after treatment with 131-I (24-26), although it is unclear whether this decrease is transient or permanent or even clinically relevant (21, 26). AMH levels show a greater decrease after 131-I in women aged 35 or older during treatment (25).

There is a need for well-defined and systematically performed studies regarding effects on long-term fertility in female survivors of *childhood* DTC. Therefore, the primary aim of the current study was to assess the reproductive characteristics (pregnancies, number of live births, pregnancy outcomes, and health of offspring) in female survivors of *childhood* DTC treated with 131-I. The secondary aim was to compare AMH levels (as a

measure of ovarian reserve) in female survivors of childhood DTC with a group consisting of women who had not been treated for cancer.

Materials and Methods

This research is part of a nationwide, long-term follow-up study on childhood DTC in the Netherlands, previously described in detail (27). The Institutional Review Board of the University Medical Center Groningen approved the study on behalf of all participating institutions (ABR NL40572.042.12, file number 2012/183). This study has been registered in the Netherlands Trial Registry (trial registration number 3448). Written informed consent was obtained from all subjects prior to participation in the study.

Participants

DTC survivors

Included were female patients diagnosed with DTC between 1970 and 2013 at age ≤18 years and treated in the Netherlands. Treatment most commonly consisted of total thyroidectomy, 131-I, and TSH suppression therapy (27). Specific exclusion criteria in this study were: less than five years since diagnosis, diagnosis of other malignancy before or after the DTC diagnosis, thyroid hormone withdrawal or recombinant human TSH administration within three months before evaluation, not being able to complete a Dutch questionnaire, and not being treated with 131-I for DTC. Patients were evaluated from February 2013 until November 2014.

Fertility assessment

Fertility was assessed by means of a self-administered questionnaire, information from medical records, and a hormonal evaluation.

Questionnaire

Survivors were asked to complete a questionnaire regarding their use of current medication (thyroid hormone, contraceptives or other medication), smoking, and reproductive characteristics: obstetric and gynecological medical history (menarche, menstrual cycles, age at first pregnancy, children conceived, birth defects and major health problems, and visiting a fertility clinic due to problems with conceiving). Survivors aged <18 years during evaluation received an altered questionnaire without questions regarding pregnancy and pregnancy outcomes.

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Medical data

Medical records were accessed to obtain information regarding survivors' characteristics: thyroid carcinoma histology, tumor node metastases (TNM) classification (redefined to the 7th edition of the TNM, since the 7th edition was current during initial evaluation), treatment modalities (type of surgery and details of 131-I administrations), and survivors' outcomes (remission, recurrence, or persistent disease, defined as previously described (27)). Co-morbidities interacting with fertility (e.g. endometriosis or gynecological surgery) were also documented.

Clinical evaluation

Survivors were evaluated during a visit to an outpatient clinic, in the context of the study of long-term treatment effects. Height and weight were measured by one of the researchers (MKH). Fasting blood samples were drawn by venipuncture. Blood samples were subsequently stored in a -80°C environment until processed. Blood sampling was performed at a random time during the menstrual cycle for logistical reasons. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) measurements were performed in survivors who did not use contraceptives containing hormones.

AMH, LH, FSH, and E2 analyses of DTC survivors were centrally performed in one run in the laboratory of the University Medical Center Groningen, the Netherlands by electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas analysis platform. Limit of detection (LoD) and intra-assay variation of these assays were 0.010 µg/L and <1.3% for AMH, 0.3 IU/L and <1% for higher ranges and 2.2% for values below 1.0 IU/L for LH, 0.100 IU/L and <2.5% for FSH, and for E2 a LoD of 0.018 nmol/L and an intra-assay coefficient of variability (CV) of 1.1-1.6% over the measuring range, whereas values below 0.07 nmol/L had a CV of 2.4-6.7%. Reference norms per age group (in years) for AMH (in µg/L, 2.5th to 97.5th percentile) were: 15 to 18.9: 0.34 – 10.39; 20 to 24: 1.22 – 11.7; 25 to 29: 0.89 – 9.85; 30 to 34: 0.58 – 8.13; 35 to 39: 0.15 – 7.49; 40 to 44: 0.03 – 5.47; 45 to 45: 0.01 – 2.71 (28, 29). Smoking and body mass index (may) may influence AMH levels and were therefore also evaluated (30-33).

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Comparison group for AMH levels

The comparison group consisted of sisters of childhood cancer survivors (n = 196) and women from the general population (n = 224) who participated in a previous nationwide cohort study among Dutch female five-year survivors of childhood cancer aiming to evaluate the effects of childhood cancer treatment on fertility (the DCOG-LATER VEVO-study (34, 35). Participants of the comparison group were aged ≥18 years and had not been treated for cancer.

AMH analyses of the comparison group were performed in one run, using an ultra-sensitive Elecsys AMH assay (Roche Diagnostics GmbH, Mannheim, Germany) in the laboratory of the VU Medical Center Amsterdam, the Netherlands. The LoD of this assay was 0.01 µg/L, the intra-assay CV of this assay was 0.5% -1.8%, and the limit of quantitation of 0.03 µg/L. Reference norms per age group (in years) for AMH (in µg/L, 2.5th to 97.5th percentile) were: 15 to 25: 0.26 – 11; 25 to 30: 0.49 – 14; 30 to 35: 0.14 – 13; 35 to 40: <11; 4 to 45: <6; 45 and older: <0.48. There was a good agreement between the two AMH assays. The Passing-Bablok regression intercept did not differ significantly from 0 (-0.003, 95% confidence interval: -0.075 to 0.021) and slope 1.092 (95% confidence interval: 1.049 to 1.143).

Study definitions

Evaluation date was the date of blood sampling or, in case of lacking blood sample, the date of filling in the questionnaire. Follow-up time was defined as the period between the date of diagnosis and the date of evaluation. Dosages of 0.9 GBq (25 mCi) or higher 131-I were considered as therapeutic doses. Women were considered postmenopausal if they reported 12 months of amenorrhea without any other obvious pathological or physiological cause (36). Premature ovarian insufficiency (POI) was defined as start of menopause before the age of 40 years (36).

Statistical analysis

Descriptive statistics regarding disease, treatment, reproductive characteristics and AMH levels are presented as median (interquartile range), unless otherwise specified. Cut-off scores for 'low AMH levels' were calculated, based on the 10th (0.22 µg/L) and 25th percentile (0.64 µg/L) of AMH levels of the complete comparison group. Categorical variables were compared using χ^2 tests or Fisher's exact tests (if >20% of the cells had an

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expected count of <5). Mann–Whitney *U* tests were performed for non-normally distributed continuous or ordinal variables. When variables were normally distributed, an independent sample *t*-test was performed. To correlate two non-normally distributed continuous and/or ordinal variables, Spearman's rank correlation coefficient (r_s) was used. Simple linear regression analysis was performed to evaluate associations between age (in years) and cumulative 131-I dose (in GBq) as predictors and AMH as outcome measure. In the first multiple linear regression analysis, log transformed AMH was predicted by attained age in years and group (coded as 0=comparison group, 1=DTC survivors). A second multiple linear regression analysis predicted log transformed AMH by independent variables: attained age (years) and cumulative dose of 131-I (in GBq). A *P* value of <0.05 was considered statistically significant. All tests were performed two-sided. IBM SPSS Statistics version 23.0.0.3 for Windows (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

Participants

Sixty-two of the 105 survivors of the nationwide follow-up study were eligible for this substudy. Four survivors declined participation and two were late for inclusion. Thus, 56 out of 62 (90.3%) female survivors were included (Supplementary Figure 1). Two of the 56 subjects only completed the questionnaire, declining participation in the clinical evaluation. Table 1 shows clinical and treatment characteristics of the included survivors. The median age of survivors at evaluation was 31.0 years (interquartile range 25.1 to 39.6 years) after a median follow-up period of 15.4 years (interquartile range 8.3 to 24.7 years). The median cumulative activity of 131-I administered was 7.4 GBq/200.0 mCi (interquartile range 3.7 to 13.0 GBq/interquartile range 100.0 to 350.0 mCi, respectively). Half of the survivors received multiple administrations of 131-I.

Reproductive characteristics

Fifty-six DTC survivors reported their reproductive characteristics in the administered questionnaire (Table 2). Four (7.1%) women reported being postmenopausal. Ages at menopause were 45, 51, and 52 years, with one age at menopause missing. Of the 55 survivors aged ≥18 years during evaluation, 25 (45.5%) reported one or more pregnancies. The median age at first pregnancy was 25.5 years (interquartile range 22.5 to 30.0 years).

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Sixty-four pregnancies were reported (2.6 pregnancies per survivor who reported to ever having been pregnant) of which 1 was a twin pregnancy. Subsequently, 45 live births were reported. Other pregnancy outcomes were miscarriage (n=13), induced abortion (n=3), unknown outcome (n=3) and pregnant at evaluation (n=1). Six survivors (10.9%) had visited a fertility doctor or clinic because of problems conceiving. Birth defects and major health problems of children reported by the survivors are shown in Supplementary Table 1.

Hormonal evaluation

Characteristics and AMH levels of the female survivors of childhood DTC and the comparison group are shown in Table 3. DTC survivors who provided blood samples had a median age of 29.4 years (n = 54, interquartile range 24.8 to 38.3 years) upon evaluation. The median age of the comparison group was 33.1 years (interquartile range 26.8 to 39.3 years). There were no statistically significant differences between the two groups for nationality (predominantly Dutch, *P* = 1.000, data not shown), age upon evaluation, smoking, and body mass index. Median AMH levels did not differ between DTC survivors and the comparison group (2.0 µg/L vs 1.6 µg/L, respectively. *P* = 0.244).

The cumulative dosage of 131-I did not correlate with AMH levels (r_s = 0.210, *P* = 0.130). In the DTC group, age was negatively correlated with AMH levels (r_s = -0.480, *P* <0.001).

Eight (14.8%) and 10 (18.5%) of the DTC survivors had an AMH-level below the cut-off value based on the 10^{th} and 25^{th} percentiles of the comparison group, respectively. The number of DTC survivors with 'low AMH levels' did not significantly differ from those in the comparison group (*P* = 0.278 and *P* = 0.296, respectively); see Supplementary Table 2.

Because the data of AMH were positively skewed, the values were log transformed. Subsequently, all assumptions for linear regression analysis were met. Log transformed AMH levels did not differ between DTC survivors and the comparison group (median ln(AMH) 0.7 vs. 0.5, respectively. *P* = 0.696, see Table 3). Results of the simple and multiple linear regression analyses for log transformed AMH are shown in Table 4. Simple linear regression showed that age was a significant predictor of log transformed AMH, but cumulative dose of 131-I was not. The first multiple linear regression analysis showed that

age was a significant predictor of log transformed AMH, but group (*i.e.* survivor vs comparison group) was not. In model 2, when log transformed AMH levels in only DTC survivors were predicted by age and cumulative dose of 131-I, age remained a significant predictor of log transformed AMH, but cumulative dose of 131-I was not.

There was no difference in AMH levels between DTC survivors who did or did not use contraceptives containing hormones, or between survivors who had received single or multiple doses 131-I (data shown in Supplementary Table 3). LH, FSH, and E2 levels of DTC survivors who did not use contraceptives or used non-hormonal contraceptives, obtained at a random time during the menstrual cycle, were within the reference range (Supplementary Table 5).

Discussion

The current study, focusing on various aspects of female fertility after treatment with 131-I for childhood DTC, shows no major abnormalities in reproductive characteristics and no difference in AMH levels between long-term DTC survivors and a comparison group after a median follow-up period of 15 years.

In this unique series of patients, the number of live births per pregnancy in the current study is comparable to those in the normal population: 70% of pregnancies in the DTC survivors resulted in a live birth, which corresponds with the 71% in an earlier prospective register based study (37). The 10% of female DTC survivors who visited a fertility clinic or doctor because of problems with conception corresponds with that of other couples in the Netherlands who are trying to become pregnant, in whom this percentage is around 15% (38, 39).

Comparing current results to findings of previous studies among survivors of *childhood* DTC is complicated by the fact that the earlier studies lack concrete definitions, report on only a small number of patients, or evaluated only a selection of reproductive characteristics (9, 13). The cumulative dose of 131-I administered to the current survivors is similar to the dose administered in the study of Sarkar et al. (13). Overall, no clear impairments of fertility have been observed in the current or previous studies in female survivors of childhood DTC (9, 13).

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It is unclear whether adverse effects of 131-I have similar consequences in *children* and in *adults*. Quantitatively, damage to the ovaries caused by 131-I could be relatively less severe in younger women, since girls and adolescent women still have a greater number of primary oocytes/primordial follicles than adult women (40). As oocytes decrease in quality with increasing age (41), a higher quality of primary oocytes/primordial follicles in pre-adult women may also be beneficial. Studies in women aged >35 years who were treated with 131-I for DTC observed a more pronounced negative effect on AMH levels (25) and birth rates (14). Negative effects on fertility in women treated with chemotherapy for other types of cancer also increase with age at treatment (42).

In this group of *childhood* DTC survivors, evaluation of AMH levels is a measure for ovarian reserve, and this hormone is not significantly affected by menstrual cycle variations (22, 23). However, as AMH levels are strongly affected by age, we adjusted our analyses accordingly.

The mere determination of AMH levels as outcome measure in the assessment of female fertility provides an incomplete representation. AMH levels have been shown to be decreased up to one year after treatment with 131-I for DTC in adults (24, 25). This reflects damage to the secondary and early antral follicles of the ovary, since AMH expression is highest during these follicular stages (Supplementary Table 5 (43, 44)). Primordial follicles are probably less prone to the effects of 131-I treatment and these unharmed primordial follicles can subsequently develop into secondary and early antral follicles after therapy, resulting in normal AMH expression over the long term. A slight rise in AMH levels in survivors of *adult* DTC one year after 131-I treatment was seen in only one study (24); this was not confirmed in another study (25). Seven years after treatment at *adult* ages, AMH levels did not differ between 131-I treated females and their controls (21). In the current study, 15 years after treatment during *childhood*, AMH levels were similar to those of the comparison group. Moreover, studies have also reported recovery of AMH levels after other anti-cancer treatments (45-47). Evaluation of AMH levels soon after treatment may indicate some form of ovarian damage, but long-term evaluation of AMH levels, combined with reproductive characteristics, are more appropriate in providing information on possible irrecoverable damage to the ovary and subsequent reproductive health.

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Unfortunately, we did not evaluate the effects of TSH suppression therapy on fertility in the current survivors (27), although effects of subclinical hyperthyroidism on fertility have not been proven (48, 49), other than the well-known effects of overt hyperthyroidism causing, for instance, menstrual disturbances, or amenorrhea (50).

Strengths of the present study include the cohort size, given the rarity of DTC in childhood, and the availability of an appropriate comparison group for AMH levels. Minor limitations deserve consideration as well. The reported reproductive characteristics may be subject to change since many of the evaluated survivors in this study were of reproductive age, but may not have conceived yet owing to other factors. The chosen reproductive characteristics were well defined, based on current knowledge. Thereby, we evaluated a broad range of reproductive characteristics that determine fertility, including objective outcome measures, such as live births and hormonal evaluation.

Although no major impact on fertility after 131-I treatment for childhood DTC was observed, this does not necessarily imply that 131-I can be administered without restriction in young female patients. Sparse data show that 131-I therapy seems to have no adverse effects on the risk of congenital abnormalities in offspring of DTC survivors (51). Other adverse effects of 131-I (*i.e.* salivary gland dysfunction, bone marrow suppression) do increase with multiple or higher doses (11, 12). This study, in accordance with previous studies, did not find a dose-response relationship between cumulative administrated 131-I and the level of AMH measurements (21, 24, 25). Follow-up beyond menopause of the survivors in this cross-sectional study will shed light on the full reproductive period. The current study can serve as a basis for this evaluation.

To conclude, the current study found no abnormalities in fertility in long-term female survivors of childhood DTC. Our conclusions are based on evaluation of a broad range of reproductive characteristics: fertility outcomes, parameters of reproductive health, indications of impaired fertility, and AMH as a marker of ovarian reserve. Altogether, these results regarding long-term reproductive outcomes seem to be reassuring for females receiving 131-I for childhood DTC.

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Table 1. Characteristics of survivors of childhood DTC

	n = 56
Age at evaluation [years]	31.0 (25.1-39.6)
Age at diagnosis [years]	16.0 (13.7-17.5)
Follow-up duration [years]	15.4 (8.3-24.7)
Histology, n (%)	
Papillary	47 (83.9)
Follicular	9 (16.1)
Tumor-node-metastasis stage, n (%)	
T	
T1-T2	37 (66.1)
T3-T4	11 (19.6)
Tx	8 (14.3)
N	
N0	27 (48.2)
N1	25 (44.6)
Nx	4 (7.1)
M	
M0	45 (80.4)
M1	6 (10.7)
Mx	5 (8.9)

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Cumulative 131-I activity [GBq][a]	7.4 (3.7-13.0)
Cumulative 131-I activity [mCi][a]	200.0 (100.0-350.0)
Multiple 131-I administrations, n (%)	28 (50.0)

Abbreviations; DTC, differentiated thyroid carcinoma.

Numbers shown as median (interquartile range).

[a] dose of administered 131-I unknown in 1 survivor, therefore n=55

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Table 2. Reproductive characteristics of survivors of childhood DTC

	n = 56
Age at menarche [years][a]	13.0 (12.0-13.0)
Postmenopausal, n (%)	4 (7.1)
Use of contraceptives, n (%)	
Hormonal contraceptives	24 (42.9)
Non-hormonal contraceptives[b]	1 (1.8)
No contraceptives	31 (55.4)
Visited doctor for subfertility (yes), n (%)[c]	6 (10.9)
Ever been pregnant (yes), n (%)[c]	25 (45.5)
Age at first pregnancy [years][c,d]	25.5 (22.5-30.0)
Number of pregnancies, n[c]	64[e]
Live births, n	45
Women reporting miscarriage, n	8[f]
Induced abortion, n	3
Pregnant during evaluation, n	1
Unknown pregnancy outcome, n	3

Abbreviations DTC, differentiated thyroid carcinoma.

Numbers shown as median (interquartile range).

[a] n=55 because one missing value.

[b] copper intrauterine device.

[c] not applicable in one participant because age <18y during evaluation, n=55.

[d] n=22 because age first pregnancy missing for 3 participants.

[e] 1 twin pregnancy

[f] 7 women reported 1 miscarriage, 1 woman reported 6 miscarriages.

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Table 3. AMH levels in survivors of childhood DTC compared to the comparison group

	DTC survivors	Comparison group	*P* Value
	n = 54[a]	n = 420	
Age at evaluation [years]	29.4 (24.8– 38.3)	33.1 (26.8 - 39.3)	0.268[b]
Smoking, n (%)			0.392[c]
Current	7 (13.0)	78 (18.6)	
Ever	13 (24.1)	123 (28.8)	
Never	33 (61.1)	221 (52.6)	
Missing	1 (1.9)	0 (0)	
Body Mass Index [kg/m^2]	23.8 (21.2 – 26.8)[d]	23.0 (21.2 – 25.9)	0.428[b]
Type of control, n (%)			
General population	-	224 (53.3)	
Sister	-	196 (46.7)	
AMH level [µg/L]	2.0 (1.0 – 3.7)	1.6 (0.6-3.1)	0.244[b]
ln(AMH)	0.7 (0.0-1.3)	0.5 (-0.4-1.1)	0.696[e]

Abbreviations; DTC, differentiated thyroid carcinoma; AMH, Anti-Müllerian Hormone.

Numbers shown as median (interquartile range).

[a] two participants participated only in questionnaire part of study.

[b] Mann-Whitney U test; [c] Pearson Chi-Square Test (Asymptotic Significance).

[d] Length and weight self-reported by 2 participants. [e] Independent samples *t*-test.

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Table 4. Simple and multiple linear regression analyses for log transformed AMH in 54 survivors of childhood DTC

Variable	intercept	β[a]	95% CI	R^2	*P* Value
Simple linear regression					
Age at evaluation [years]	4.12	-0.12	-0.13; -0.11	0.418	<0.001
Cumulative 131-I activity [GBq]	-0.28	0.06	-0.01; 0.12	0.056	0.089
Multiple linear regression					
1. Age at evaluation [years]	4.13	-0.12	-0.13; -0.11	0.418	<0.001
Group[b]		-0.06	-0.40; 0.29		
2. Age at evaluation[years][c]	3.73	-0.12	-0.16; -0.07	0.414	<0.001
Cumulative 131-I activity [GBq]		0.02	-0.04; 0.07		

Abbreviations; AMH, Anti-Müllerian Hormone; DTC, differentiated thyroid carcinoma.

[a] Unstandardized coefficients β

[b] comparison group = 0, DTC survivors = 1

[c] 'Group' removed from this analysis, because comparison group did not receive 131-I administrations

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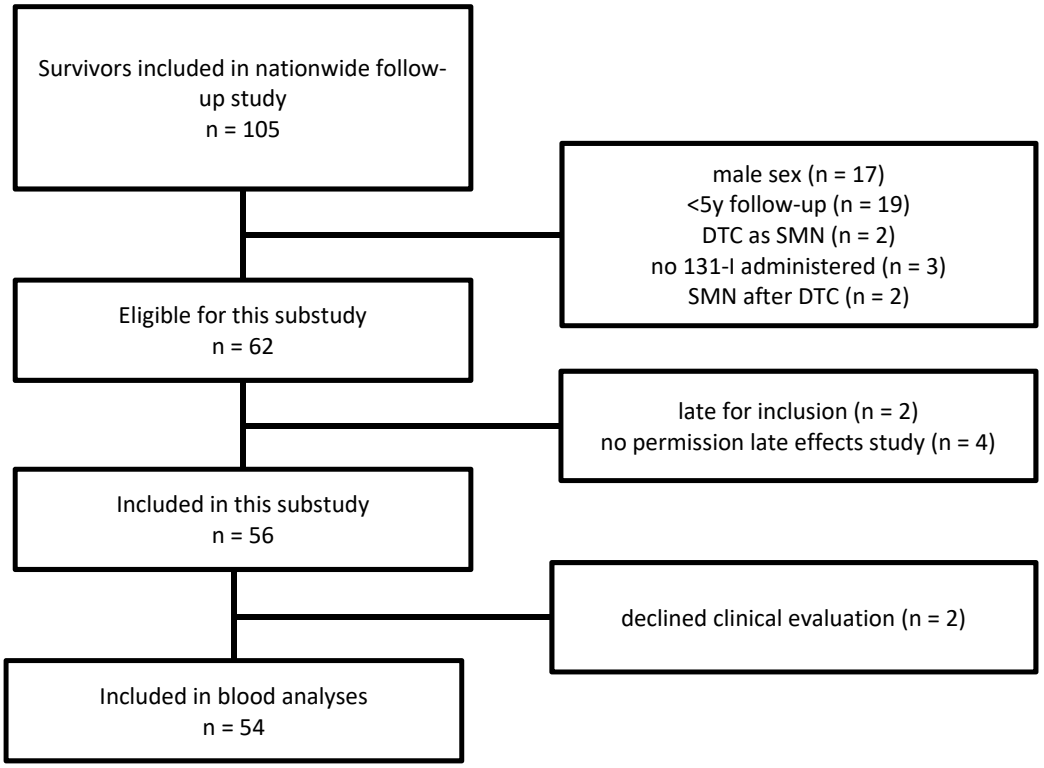
Supplementary material



Supplementary Figure 1. Flowchart of inclusion

Supplementary Table 1. Parentally self-reported birth defects and major health problems in 45 children of survivors of childhood DTC

Reported health problem	**n**
Dilated ureter by birth	1
Blount disease	1
PDD-NOS	1
Lung tumor	1
Hypermobile Ehlers-Danlos syndrome	2[a]
Facial paralysis	1
Total	**7**

Abbreviations; DTC, differentiated thyroid carcinoma; PDD-NOS; pervasive developmental disorder-not otherwise specified.

[a]Children from the same mother.

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Supplementary Table 2. Percentages of DTC survivors with low AMH based on 10th percentile and 25th percentile of comparison group

	DTC survivors n = 54[a]	Comparison group n = 420	*P* Value
10th percentile, n (%)[b]			0.278[c]
Low AMH	8 (14.8)	42 (10.0)	
No low AMH	45 (85.2)	378 (90.0)	
25th percentile, n (%)[d]			0.296[c]
Low AMH	10 (18.5)	105 (25.0)	
No low AMH	44 (81.5)	315 (90.0)	

Abbreviations; DTC, differentiated thyroid carcinoma; AMH, Anti-Müllerian Hormone.

[a] two participants participated only in questionnaire part of study.

[b] threshold 10th percentile = 0.22 µg/L

[c] Pearson Chi-Square Test (Asymptotic Significance).

[d] threshold 25th percentile = 0.64 µg/L

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Supplementary Table 3. AMH levels in subgroups of survivors of childhood DTC

	No hormonal contraceptive n = 30	**Hormonal contraceptive** n = 24	***P* Value**
AMH [µg/L]	2.3 (0.7-3.7)	1.9 (1.2-3.8)	0.676[a]
	Single dose 131-I n = 28	**Multiple doses 131-I** n = 26	
AMH [µg/L]	1.5 (0.4-3.6)	2.3 (1.3-3.9)	0.319[a]

Abbreviation; AMH, Anti-Müllerian Hormone; DTC, differentiated thyroid carcinoma.

Numbers shown as median (interquartile range).

[a] Mann-Whitney U test.

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Supplementary Table 4. Hormonal evaluation in survivors of differentiated thyroid carcinoma during childhood not using hormone contraceptives

	n = 30
Hormone	
Follicle-stimulating hormone [IU/L]	5.4 (3.2-13.2)
Luteinizing hormone [IU/L]	8.6 (4.5-14.9)
Estradiol [nmol/L]	0.4 (0.1-0.7)

Numbers are shown as median (interquartile range).

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Supplementary Table 5. Folliculogenesis and AMH secretion

Follicular stage	AMH secretion
Primordial follicle	-
Primary follicle	+
Secondary follicle	++
Early tertiary/ antral follicle	+++
Late tertiary/pre-ovulatory follicle	-

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