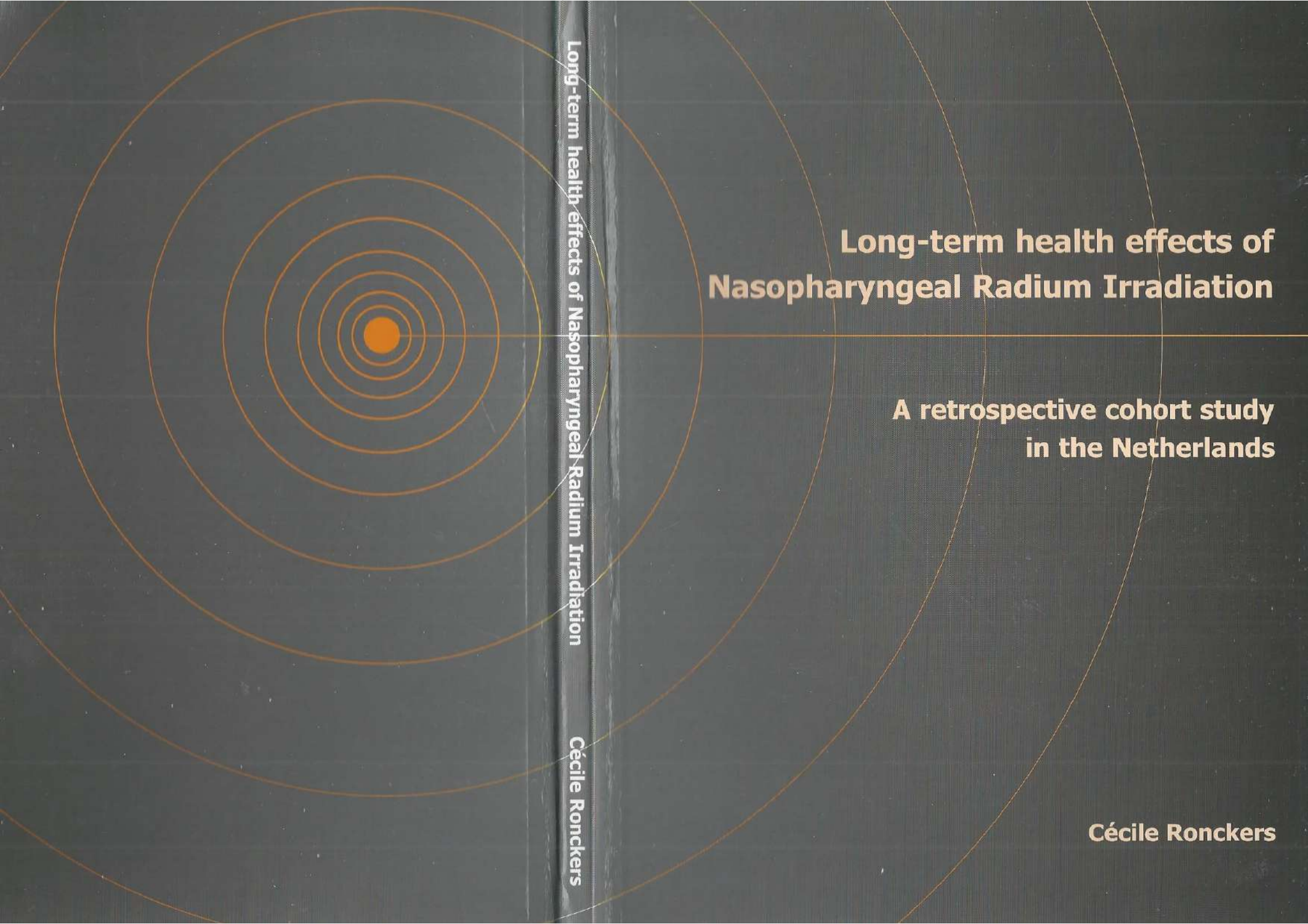
Long-term health effects of Nasopharyngeal Radium Irradiation
Cécile Ronckers
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A retrospective cohort study
in the Netherlands
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A retrospective cohort study in The Netherlands

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Long-term health effects of nasopharyngeal radium irradiation

A retrospective cohort study in The Netherlands

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CONTENTS

1

Introduction

Introduction

This thesis presents background, methodological aspects, results, and a critical appraisal of a follow-up study of the long-term adverse health effects of nasopharyngeal radium irradiation in The Netherlands. This now abandoned form of treatment for Eustachian tube dysfunction was widely used by ear, nose, and throat physicians in the decades following WW-II, in the US, Canada and several European countries [1-3].

Historical perspective

Just before the end of the 19th century, in 1895, Röntgen first described X-rays [4]. Soon thereafter, X-rays were introduced into medicine and came into widespread use for therapeutic applications as well as diagnostic imaging. Between 1895 and 1910, X-rays were used to treat a variety of skin disorders, hypertrichosis (excessive growth of hair) as well as breast and cervical cancer [reviewed in 5]. From the 1920s onwards, external X-ray therapy was subsequently used to treat benign disorders, such as (presumed) enlargement of the thymus, tinea capitis, tonsillar enlargement, cervical lymphadenitis, and acne [6-8]. None of these benign conditions, however, would be treated with X-rays in contemporary medicine. By contrast, diagnostic imaging through X-rays and treatment of malignant disorders (e.g., cervical cancer, Hodgkin's disease) [9,10] with external beam therapy are examples of ongoing use of X-rays in standard medical practice currently. With regard to non-medical use of X-rays, Hempelmann (1948) [11] described fitting children's shoes with use of X-ray devices.

Shortly after Röntgen's discovery of X-rays, Pierre and Marie Curie discovered polonium [12] and radium [13]. Radium (atomic number 88) is one of the elements in the radioactive decay process from uranium to the stable element lead. A well-known radium decay product is the radioactive gas radon [14]. In the early 1900s, drinking of radon-containing water was advocated to cure liver disorders and rheumatic conditions [15]. For this purpose, a radium goblet was used, i.e., a metal cup containing a radium source, to "contaminate" water with radon [15]. Radium was used as an external radiation treatment source to treat hemangioma and basal cell carcinoma (BCC) of the skin [5,16]. Internal use (brachytherapy) included nasopharyngeal implants [17] (see below) and radium implants in female reproductive organs to treat cervical cancer, the so-called "vaginal bomb" [15]. In Germany, Radium-224 was injected into bone, to treat ankylosing spondylitis and bone tuberculosis [18]. In industry, small amounts of radium

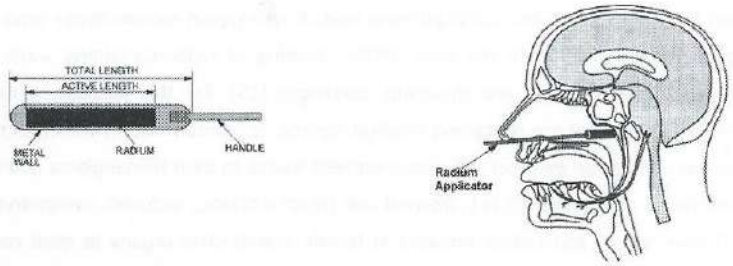
were added to paint, which was then applied to watches and instruments to create luminescent dials [reviewed in 19].

Nasopharyngeal radium irradiation

It was in this era of acknowledgement and appreciation of the beneficial characteristics of radiation for medicinal use that Dr. Samuel James Crowe developed the concept of nasopharyngeal radium irradiation for treatment of persistent ear-nose-throat (ENT) disorders in children, conditions that were otherwise hard to control.

In 1924, Crowe was awarded funds to develop a research laboratory for the study of hearing disorders in children [20]. Subsequently, in 1939, Crowe and Baylor [21] described their observation that recurring enlarged adenoids and serous otitis were associated with childhood deafness, with the potential of persisting deafness into adulthood. The condition was characterized by "overgrowth of lymphoid tissue in and around the pharyngeal orifice of the Eustachian tubes" [21] as a reaction to upper airway infections, mainly seen in children between 5 and 10 years of age. Upon reaching pubertal ages, the reactivity of the lymphoid tissue to infections diminishes greatly. Therefore, Crowe focussed on finding a treatment for young children that would reduce the overgrowth of lymphoid tissue until they reached puberty, thereby re-opening the blocked airways to the Eustachian tubes and preventing both temporary deafness and deafness persisting into adulthood. Surgical removal of all recurring lymphoid tissue was not possible without damage to surrounding structures [21].

Being aware of a report on the high radiation sensitivity of lymphoid tissue compared to surrounding tissues [22], Crowe proposed to use local radiation treatment to reduce the size of the lymphoid tissue overgrowth and to temporarily inhibit its growth, until the child had reached



Figures 1.1 and 1.2
Diagrams of radium tube used for nasopharyngeal radium irradiation and its position in the nasopharynx during treatment [23]

puberty [21]. The recommended nasopharyngeal radium irradiation (NRI) treatment consisted of three sessions in which an applicator containing 50 mg of radiumsulphate (Figure 1.1) was inserted through the nostril into the nasopharynx for 8½ minutes on each side [17]. Figure 1.2 shows a schematic illustration of the location of the radium capsule during an NRI treatment session. In a newly manufactured radium applicator, radium reached equilibrium with its daughter products within 30 days, and then emitted α-particles (i.e., positively charged, heavy and slow traveling helium nuclei), β-particles (negatively charged, light electrons) and γ-rays. The applicators had walls made of 0.3-mm monel, a metal alloy, which fully blocked α-particles. The treatment effect was mainly accomplished by β-particles, which can only penetrate tissues within 10 mm of the source (i.e., from the nasopharynx). The Monel-filter also allowed passage of γ-rays, which are deeply penetrating waves that are responsible for radiation doses in tissues at distances greater than 10 mm from the radium source (reviewed in [23]). It was estimated that

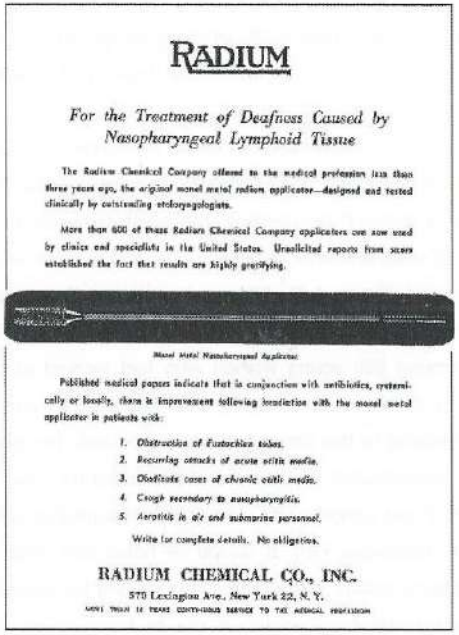

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Figure 1.3
Advertisement for the use of radium applicators in ENT medicine

75 percent of all radiation emitted from the radium source was absorbed in the first 3 mm of tissue depth, i.e., mainly in the lymphoid tissue that needed to be shrunk [17,23].

Numerous reports, including clinical series and a few randomized trials [24], have been published on the efficacy of NRI in the management of recurrent ear infections and the prevention of deafness [reviewed in 2,25]. Figure 1.3 shows an advertisement used to recommend NRI to physicians in the early years. In the US, NRI was also successfully applied in WW-II military personnel to treat aerotitis media (barotrauma), a condition caused by frequent air pressure changes in submariners and aviators [3,26,27].

Long-term side effects of radiation exposure

Shortly after the discovery of X-rays and radium, case-reports on adverse effects of radiation exposure among chronically exposed scientists and physicians were published, i.e., eye problems and also skin dermatitis [reviewed in 5,6]). In 1902, Frieben [28] reported on a squamous cell carcinoma (SCC) on the hand of a radiologist, which is thought to be the first published report of a radiation-induced cancer. By 1936, a (worldwide) total of 169 fatalities were attributed to radiation-exposure at work, of which 75 percent involved skin cancer [6].

Radium dial painters represent another group of workers who were exposed to radiation from 1913 onwards. Until this practice was officially banned in 1926, the mainly young, female painters had the habit of "tipping" or "pointing" the brush between the lips before applying the paint to the dial, so that small amounts of radium-226 (and in some factories also mesotherium, radium-228) were ingested (Figure 1.4). After early case-reports on osteomyelitis and anemia, Martland in 1929 [29] reported on 18 deaths, including 5 (i.e., 27 percent) deaths from osteogenic sarcoma, among 800 young women who had worked as dial painters. Substantial amounts of radium were present in their bones, and, based on an autopsy series, less than 0.1 percent of deaths attributable to this tumor had been expected. Ten years later, elevated risk of 'head carcinoma' was demonstrated, i.e., tumors of the epidermal lining of the paranasal sinuses or the mastoid process. These tumors were seen only in radium-226 exposed painters, and were ascribed to exposure to radon gas [30]. It should be noted that most, although not all, of the elevated cancer risk among radium dial painters was caused by internally deposited radium (in bone) that continuously emitted α-particles in the body [reviewed in 19]. Other malignant diseases that were recognized to be associated with occupational radiation exposure included leukemia in radiologists and lung cancer in uranium miners [5].

Although cancers had also been reported among patients who had been treated with radiation therapy previously, it was generally thought that cancers would arise only in macroscopically damaged tissue (e.g., skin cancer after radiodermatitis or leukemia after

anemia), and that lowering the radiation dose to levels not causing acute effects would protect the patient against the risk of radiation-induced cancers [5].

Nevertheless, Duffy and Fitzgerald [31] in 1950 described nine children with thyroid cancer who had received X-ray treatment for thymic enlargement in infancy. Their hypothesis of an etiologic role of childhood radiation therapy in the development of thyroid cancer was soon supported by other reports [32,33].

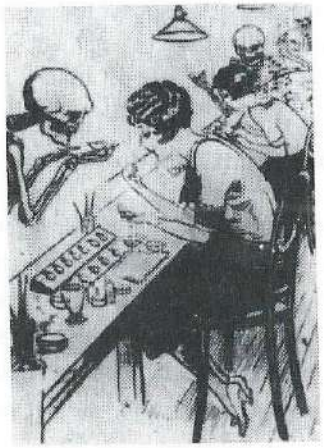

Figure 1.4
New York newspaper cartoon alluding to the radium poisoning of watch dial painters [34]

Simultaneously, reports on mortality and morbidity in the Japanese population exposed to the 1945 atomic bomb explosion, and the 1954 US nuclear weapon tests, added to growing concern about possible long-term adverse effects of radiation exposure [5]. Reports by the US National Academy of Sciences - National Research Council [35] in 1956 and the UK Medical Research Council [36] in 1960 recognized the need for long-term follow-up of populations exposed to radiation, both in medical and non-medical settings. The Life Span Study among 120,000 residents of Hiroshima and Nagasaki was initiated soon thereafter, and remains a major

source of information on the spectrum of adverse health following radiation exposure [37]. Many occupationally, environmentally and medically exposed populations have been defined and studied since. A full literature review on late effects of radiation exposure falls beyond the scope of this thesis. Extensive reviews on the available populations and research results were recently published [38-40].

The following brief literature review on late effects of radiation exposure is focused on populations treated for benign head and neck disorders in childhood. The following section first provides a brief introduction to the basic concepts of the quantitative aspects of both radiation exposure and risk.

Quantification of radiation dose

Radiation exposure was traditionally expressed in röntgen (R), which represents the total charge of ions of one sign produced in air per unit of mass. However, as the röntgen is not applicable to all types of radiation and does not include the interaction between tissue and radiation, in 1953 the rad was proposed, which measures absorbed energy, or dose. One rad is defined as 100 ergs per gram of matter (the material that is being irradiated, e.g., air, tissue). It has been replaced by the SI unit, the gray (Gy), which represents 1 Joule of energy absorbed in each kilogram of absorbing material (1 Gy = 100 cGy = 100 rad).

When electromagnetic radiation (X-rays, γ-rays) or particles from radioactive decay (α-particles, β-particles) interact with a given tissue, energy or mass and electrical charge determine the depth of penetrance into the tissue and the amount of energy deposited in tissue. The latter can be measured as a function of distance along the track of radiation in the tissue. Ionizing radiation is divided into high-LET (α-particles) and low-LET (X-rays, γ-rays, β-particles); LET refers to linear energy transfer, or the amount of energy deposited in a unit of track length. The biological effects of radiation depend upon the energy transferred to tissue; high-LET radiation is more effective in causing damage to biological tissues per unit of absorbed radiation dose compared to low-LET radiation.

In radiological protection the absorbed dose is therefore weighted by a factor related to the quality of the radiation [41]. The equivalent dose is the product of the absorbed dose averaged over a tissue or organ and the radiation weighting factor and is expressed in sievert (1 Sv = 100 cSv = 100 vcm). For the low-LET radiation involved in external X-ray treatments and NRI, the absorbed dose and the equivalent dose are numerically equal.

Expression of radiation-associated risk

To study the association between radiation exposure and cancer risk, one can calculate the cancer rate, i.e., the total number of observed cases divided by the total number of person-years of observation, in the radiation-exposed population and compare it to the cancer rate of a comparison group.

One type of comparison group might be the general population (external comparison group). In this type of analysis, the sex-, age-, and calendar-time specific person-year experience of the exposed group is multiplied by the appropriate cancer rates from the general population, and summed, to derive the total number of expected cancers in the exposed population. The ratio of the observed (O) and expected (E) number of cases, the so-called Standardized Mortality Ratio (SMR) is about one in absence of an exposure effect, and above one in case of elevated cancer risk. However, the general population and the studied radiation-exposed population might differ by more than just radiation-exposure. Therefore, epidemiologic studies often include an internal comparison group of non-exposed subjects who are as similar as possible to the exposed group, but were not exposed to radiation. In this type of analysis, the cancer rate in the exposed population is compared to the cancer rate in the non-exposed population in terms of the risk difference or risk ratio (or relative risk, RR). Similarly, SMR values computed for the two groups can be compared in the same way. This provides some protection in case the exposed and non-exposed groups are slightly different in terms of age and/or sex.

Ideally, one would also like to know whether there is evidence of a dose-response relationship. The cancer rates of groups exposed to different levels of radiation dose (for example medium and high dose) are then compared to cancer rates of a low-dose group, or of the non-exposed group. Alternatively, one can use a continuous dose variable, to model the RR as a function of dose (d). Often, it makes more sense to model the excess relative risk (ERR = RR - 1) as a function of dose. For example, if RR(d) increases proportionally with dose, then ERR(d)/d should be a constant.

Alternatively, excess dose-related cancer risk can be expressed in terms of the risk difference, the excess absolute risk (EAR), which is the cancer rate at dose d minus the cancer rate at dose 0 (i.e., the non-exposed group). The EAR(d) can be derived by multiplying the ERR(d) by the cancer rate at dose 0.

Although the EAR and the ERR represent the same data, they do express a different message, which might be best illustrated in an example of a study into late treatment effects among patients who were treated for Hodgkin's disease (HD) in the past. In view of the excellent cure rate for HD, studies have focused on the long-term excess risk of second malignancies (e.g., breast cancer, lung cancer, gastrointestinal cancers and, leukemia) in

Table 1.1
Follow-up studies of the long-term health effects of external X-ray therapy for benign head and neck conditions in childhood: Study Characteristics

Study /place	Ref	Study population (No.) Exposed	Non-exposed	Years of exposure	Mean follow-up (y)	Mean age at treatment (y)(range)	Mean organ doses (Gy)* (range) Brain	Thyroid gland	Parotid gland	Pituitary gland	Skin	Breast	Assessment of cancer outcome
Tinea capitis Israel	45-50	10,834	16,226	1948-1960	30	7 (0-15)	1.5 (1.0-6.0)	0.09 (0.04-0.5)		(0.48-0.66)	Scalp 6.8 (5.5-24.4)	0.016	Hospital records Cancer registry Death certificates
Tinea capitis New York††	51-54	2,215	1,395	1940-1959	37	7.9	1.4	.06	0.39	0.49	Scalp 4.8 Eyelid 0.44 Nose 0.40 Neck 0.21		Mailed questionnaires Medical confirmation
Thymic enlargement Rochester, NY	55-58	2,657	4,833	1926-1957	35	0.1 (0-1)		1.36 (0.03->10)			Scalp (3-6) Face (0.1-0.5)	0.69	Mailed questionnaires Medical confirmation Death certificates
Tonsillar enlargement MRH Chicago	59-61	2,947‡	0	1939-1962	33	4 (0-15)	4.6	0.59 (0.01-5.8)	4.2 (0.01-15.8)				Telephone interviews Medical confirmation Clinical exams
Lymphoid hyperplasia CHMC Boston	62	1,590	1,499	1938-1969	29	6 (0-18)		0.24 (0.03-0.55)					Mailed questionnaires Medical confirmation Clinical exams
Thymus/ Cerv. Adenitis Cincinatti	63-64	1,266	10,813	1932-1950	36	3.6		2.9					In-person interviews Medical confirmation Cancer registry
Tuberculous lymphadenitis Netherlands**	65-66	306	0	1920-1963	43	16 (0-49)		10.6			19.2#		Mailed questionnaires Clinical exams Death certificates
Tonsil/thymus/ acne Univ. Chicago	67	263	0	?	26	7.1		4.5			10.5		Clinical exams
Skin Hemangioma Sweden†¶$	16, 68-71	28,008	0	1920-1965	32	0.5 (0-3)	0.08 (0–11,5)	0.26 (0.01-28.5) Stockholm				0.29 (0.01-35.8)	Cancer registry

* from published reports
† 80% treated with external ^{226}Radium; 20% with X-rays
‡ in last reported follow-up [61]
# skin dose among non-cases; among skin cancer cases: 32.8 Gy
¶ pooled analyses of 2 cohorts from Stockholm [16] and Gothenburg [69]
$ weighted bone marrow dose: 0.13 Gy (range, <0.01-4.6)
** mixed juvenile and adult patients
†† average cranial bone marrow dose: 3.85 Gy ;

Table 1.2
Follow-up studies of the long-term health effects of external X-ray therapy for benign head and neck conditions in childhood: Qualitative results for malignant and benign tumors*

Study/place	Ref	Malignant disease Thyroid	Brain	Salivary gland	NMSC†	Breast	Leukemia	Benign tumors Thyroid	Brain	Salivary gland	Skin	Breast
Tinea capitis Israel	45-50	+	+	+	+	+	+	+	+	+	+	ANR
Tinea capitis New York	51-54	+	+	ANR	+	ANR	+	+	+	+	+	ANR
Thymic enlargement Rochester,NY	55-58	+	0	0	+	+	ANR	+	+	+	+	+
Tonsillar enlargement MRH Chicago	59-61	+	ANR	+	ANR	ANR	ANR	+	+	+	ANR	ANR
Lymphoid hyperplasia CHMC Boston	62	+	ANR	ANR	ANR	ANR	ANR	+	ANR	ANR	ANR	ANR
Thymus/ Cerv. Adenitis Cincinatti†	63-64	+	ANR	+	ANR	ANR	ANR	+	ANR	ANR	ANR	ANR
Tuberculous lymphadenitis Netherlands	65-66	+	ANR	ANR	+	ANR	ANR	+	ANR	ANR	ANR	ANR
Tonsil/ Thymus UC Chicago	67	+	ANR	ANR	ANR	ANR	ANR	+	ANR	ANR	ANR	ANR
Skin Hemangioma Sweden	16, 68-71	+	+	ANR	ANR	+	0	ANR	ANR	ANR	ANR	ANR

* explanation of symbols on the reported association of the specified tumor and the external radiation therapy:
+ statistically significant positive association
0 no association demonstrated (includes statistically non-significant associations)
ANR association never reported
† NMSC = non-melanoma skin cancer

survivors of HD [42,43]. A recent review [44] demonstrated that the EAR for both leukemia and breast cancer in HD-survivors was approximately 12 per 10,000 patients per year. However, the background rates for breast cancer and leukemia are very different, i.e., in absence of exposure, the number of breast cancers expected to occur is much higher than the number of leukemia cases expected to occur among HD-survivors. Therefore, *relative* to the already expected absolute numbers of cancers based on the background risk, the excess risk of breast cancer in this population is lower (ERR = 1.7) than the excess risk of leukemia (ERR = 21.3).

Adverse late health effects of X-ray treatments for benign diseases in childhood

Table 1.1 summarizes characteristics of the largest follow-up studies among subjects who were treated with external X-rays for benign head and neck disorders in childhood. Most studies were initially set-up to assess thyroid cancer risk, but as follow-up progressed, other radiation-related malignant and benign conditions were recognized.

The cohorts range in size from 263 up to 10,843 patients and represent treatments applied between 1920 and 1970 with subsequent evaluation of late effects up to 50 years after exposure. Some, but not all studies include non-irradiated controls for comparison, e.g., other patients of the same clinics where the radiation treatments were given, or siblings of the irradiated patients. Assessment of disease outcomes was typically done by tracing patients and contacting them for participation in questionnaire surveys, including medical confirmation of self-reported disorders, and/or clinical exams. Where available, tumor registries and registries of death certificates were used to determine cancer occurrences.

Table 1.2 shows qualitative results of malignant and benign tumors for the presented studies. All studies showed elevated risk of thyroid cancer. With regard to other cancer sites, i.e., salivary glands, brain, skin, and also leukemia, not all studies provided information. Among the larger cohorts that did identify substantial numbers of cancers, elevated risks are reported as well. The same holds for reports of benign tumors in head and neck tissues after external X-ray treatments.

Quantitative risk estimates for thyroid cancer have been reviewed by Shore (1992) [72] and in a pooled analysis of seven cohorts by Ron et al (1995) [73]. The pooled analysis included approximately 58,000 subjects exposed to external radiation, including cancer patients who had been treated with high-dose radiation, and approximately 61,000 non-exposed subjects. For persons exposed to radiation at childhood ages, the pooled ERR/Gy was 7.7 (95% CI: 2.1 to

28.7) and the EAR per 10,000 person-years-Gy (PY-Gy) was 4.4 (95% CI: 1.9 to 10.1) [73]. The authors also note that for subjects exposed to radiation before the age of 15 years, linearity best described the dose response, even down to 0.10 Gy. At the highest doses there was evidence of leveling or decrease of risk. This phenomenon has also been seen in other radiation-studies and is thought to be related to cell-killing, since a cell that is killed by radiation-damage cannot pass on its damaged DNA to new generations of cells, and thus cannot cause malignant deformation [39]. The ERRs from the pooled study were strongly influenced by age at treatment, in so far that subjects exposed before the age of 5 were at the highest risk of developing thyroid cancer [73].

For other cancers, quantitative risk estimates have been summarized in the 2000 UNSCEAR report [40]. For tumors of the central nervous system (CNS), the average ERR at 1 Gy was estimated to be 4.08 (95% CI: 3.1 to 5.2) in the Israel tinea capitis cohort, and 3.4 (95% CI: 1.3 to 6.7) in the New York tinea capitis cohort, whereas the average EARs per 10,000 PY-Gy were 1.2 (95% CI: 0.9 to 1.5) and 0.98 (95% CI: 0.4 to 1.9), respectively. Many of the radiation-induced CNS tumors were benign tumors, such as neurilemmomas, schwannomas and meningeomas (although the latter includes malignant subtypes) [39,46,60]. Elevated numbers of salivary gland tumors have been reported, but it is difficult to demonstrate statistically significant dose-response relationships, as these tumors are rare and, therefore, few cases were observed per cohort.

With regard to skin cancer, low-dose radiation studies mainly focus on non-melanoma skin cancer (NMSC) of which the most frequent subtypes are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Estimates of ERR/Gy for NMSC vary from 0.11 (95% CI: 0.03 to 0.19) in the Chicago tonsil cohort to 1.05 (95% CI: 0.50 to 1.9) in the thymic enlargement cohort whereas the EARs/10,000 PY-Gy range from 0.18 (95% CI: 0.1 to 0.25) for the Israel tinea capitis cohort to 2.5 (95% CI: 1.9 to 3.2) among whites only in the New York tinea capitis cohort [40]. In the latter cohort [54] risk of BCC was lower at the hairy scalp compared to skin areas without hair, i.e., skin that was not shielded to UV-exposure. As with thyroid cancer, it is thought that children are particularly susceptible to the adverse effects of external radiation on the skin [40].

In summary, it is demonstrated that external X-ray treatments at childhood ages can induce thyroid cancer, and a number of other benign and malignant tumors in the head and neck area. These results are supported by studies among cancer survivors (children and adolescents) who were exposed to high doses of radiation to the head and neck area [reviewed in 44,74].

Only a few studies report "null" results for a specific type of tumor, which might represent publication bias, as recognized by Modan [75]. The presented studies also demonstrate methodological problems in studies of late health effects of low-dose radiation exposures in

childhood. In general, radiation-induced solid tumors do not emerge in the early years after exposure, but sometimes only up to several decades after a treatment in childhood. Therefore, long follow-up periods and good tracing methods are needed to study late health effects of radiation exposure in general. Based on extrapolation of results from high-dose studies, the expected risk elevation in low-dose studies is often small. Only large cohorts have sufficient statistical power to demonstrate such effects [40,75-78].

Adverse late health effects of nasopharyngeal radium irradiation

Tissue-specific absorbed doses associated with NRI, in general, have been lower compared to the tissue doses from the external X-ray treatments described before, with the exception of the nasopharyngeal tissues in direct vicinity of the radium capsule during NRI treatment. As cited before, 75 percent of all radiation emitted from the radium applicator was absorbed in tissue within 3 mm from the applicator, i.e., within the excess lymphoid tissue to be removed. The remaining 25 percent of radiation, mainly from penetrating γ-rays, could reach other tissues in the head and neck area, such as the brain, salivary glands and thyroid, but at greatly diminished dose levels since the γ-rays rapidly loose their energy as they penetrate tissues. Nevertheless, several investigators have warned against potential adverse effects of this treatment on both physicians and patients [reviewed in 26].

It should be mentioned that Dr. Crowe stressed the need of only using NRI to treat nasopharyngeal lymphoid hyperplasia, to comply with recommended treatment times, and to keep the applicator in an appropriate shielded lead tube at all times except for use during the treatments to protect both patients and medical professionals against harmful side-effects of unnecessary radiation exposure [17].

Until the present study was started, in 1995 (i.e., this thesis), three follow-up studies addressing long-term cancer risk after NRI had been published (Table 1.3). Hazen and others (1966)[79] studied a mixed cohort of children exposed to external X-rays or NRI. Only 417 subjects were radium-exposed and, after an average follow-up of 14.6 years, only 2 cancers were observed, compared to 1.6 expected.

In 1982, Sandler and others [80] reported on a Maryland cohort of patients who where treated in the clinic that was founded by Dr. Crowe for his research on hearing disorders. Of almost 3,000 patients treated between 1940 and 1960, 904 had been exposed to NRI. The other patients were used as a comparison group. In 1981, three brain cancers and one pharyngeal cancer had occurred in the exposed group, compared to none of these cancers in the non-

Table 1.3
Follow-up studies into the long-term health effects of nasopharyngeal radium irradiation

Study /place	Ref	Study population (No.)		Years of exposure	Mean Follow-up (y)	Mean Age at treatment (y)(range)	Mean organ doses (Gy) (range)#		Assessment of cancer outcome	Findings$
		Exposed	Non-exposed				Thyroid gland	Pituitary gland		
Upstate New York county	79	417	2,716	*	14.6	11	"negligible"	(0.18-0.39)	Mailed questionnaires Medical confirmation	N=2 cancers / 1.6 expected (N=0 head neck tumors)
Washington County (MD)	80, 86, 87	904	2,021	1940-1960	50	(0 - >15)	0.09	0.78 (0.44-1.70)	Mailed questionnaires Medical confirmation Tumor registry Death certificates	Thyroid cancer RR=4.2 (95% CI 0.4-44.6) Brain cancer RR=14.8 (95% CI 0.8-286)¶ Deficit of hormone related cancers
Netherlands Multi-center	2,81	2,510	2,199	1945-1965	20-40	(0->15)	(0.02-0.07)	(0.10-0.36)	Death certificates	All deaths RR=1.0 (95% CI 0.7-1.5) All cancers RR=1.3 (95% CI 0.6-2.7) Brain cancer RR= 0.5 (95% CI 0.0-8.7) Lymphopoietic RR=2.3 (95% CI 0.4-23)
Submarine Training Center (CT)	89	1,214†	3,176	1945	51	22.5	-	-	BIRLS‡ Social security deaths file Nat. Death Index	All deaths OR=1.3 (95% CI 1.1-1.5) Head-neck cancer OR=1.4 (95% CI 0.5-3.6) Circulatory disease OR=1.5 (95% CI 1.2-1.9)

* not given, probably between 1945-1955
† ~70% known to be treated with nasopharyngeal radium irradiation
‡ BIRLS = Beneficiary Identification and Record Locator Subsystem
# from published reports
¶ based on 3 exposed cases of malignant brain tumors – in addition, 4 benign brain tumors were observed
$ RR = relative risk; CI = confidence interval

exposed group. A third study was conducted in The Netherlands that was comprised of 2,510 exposed and 2,199 non-exposed subjects, mainly treated at childhood ages, between 1945 and 1965 [2,81]. In a mortality follow-up through 1985, no significantly elevated risk of death from any cancer was demonstrated, although the standard mortality ratios (SMR) for total cancer and lymphopoietic malignancies were 1.3 and 2.3, respectively. However, confidence intervals were wide due to small numbers of cases [81].

Recent public concern

The above results from follow-up studies present the available data on NRI until the early 1990s. By that time, in the US public concern about possible late adverse effects of NRI was on the rise [82-84]. In 1995, the Centers for Disease Control and Prevention (CDC, Atlanta, GA), Yale University (New Haven, CT) and the Department of Veterans Affairs (Washington DC) organized a workshop to discuss "the public health response to nasopharyngeal radium irradiation".

To address the scope of NRI-use, CDC estimated that 0.5 to 2.0 million civilians had been treated with NRI in the US, from 1946 through 1961 [1]. In addition, at least 8,000 submariners had been treated with NRI [3]. Expert panels discussed the desired direction and methodological design for further studies into late health effects of NRI [85]. The summary panel recommended extending the follow-up of existing cohorts, as the success of any new historic cohort study would be restricted by the lack of availability of old medical records, or, in the case of the military, the lack of possibilities to identify exposed subjects and successfully trace them [85].

Therefore, follow-up of both The Netherlands study and the Maryland study was continued, and, in addition, a mortality study among a group of presumably NRI-treated submariners was pursued. Recently, results of the Maryland study and the military study were published [87,89] (Table 1.3). Yeh and others (2001) [87] observed four benign brain tumors in the Maryland cohort, in addition to the three tumors that had already been reported by Sandler and others [80]. The RR for malignant brain tumors amounted to 14.8 (95% CI: 0.8 to 286) [87]. Furthermore, two thyroid cancers among exposed subjects compared to one among non-exposed subjects were observed.

Suggestive, but statistically non-significant decreased risks were noted for hormone-dependent cancers, and the estimated RR for breast, endometrium, ovarian and prostate cancer combined was 0.39 (95% CI: 0.17 to 0.91) [87]. The authors speculated on a possible association with radiation-induced pituitary gland damage and subsequently decreased sex-hormone levels, because the pituitary gland is among the extra-nasopharyngeal tissues most

heavily exposed during NRI. There was no evidence of reproductive characteristics affected by such damage in the Maryland study [86,87], although growth hormone, gonadotropin and thyroid stimulating hormone deficiencies and all associated clinically relevant implications (e.g., reduced adult stature, early menarche, subfertility and thyroid disorders) have been described in children treated with high-dose cranial radiotherapy for brain cancer or leukemia [88].

Kang and others (2000) [89] reported elevated risk of all-cause mortality (OR=1.32, 95% CI: 1.14 to 1.53) and circulatory disease mortality (OR=1.51, 95% CI: 1.20 to 1.90) among 1,214 exposed (70 percent known to be treated with NRI) and 3,176 non-exposed submariners. In addition, a slightly elevated risk of fatal head and neck tumors was reported (RR=1.40, 95% CI: 1.20 to 1.90). Tumor-specific results were not presented [89].

In this thesis the updated follow-up of The Netherlands cohort is reported. We doubled the cohort size by including subjects treated with NRI between 1945 and 1981 for whom old medical treatment records were still available in the medical file archives of ENT physicians in The Netherlands.

The Netherlands cohort study on late health effects of nasopharyngeal radium irradiation

Research aims

The Netherlands cohort study on late health effects of nasopharyngeal radium irradiation was aimed to examine the following measures of outcome:

- Cancers of the head and neck area (including thyroid, brain, salivary glands and nasopharynx)
- Hematopoietic and lymphoproliferative malignancies
- Hormone-related cancers, including breast and prostate cancer [80,87]
- Non-melanoma skin cancers
- Benign tumors of the head and neck area
- Thyroid disorders
- Conditions related to regulatory control of anterior pituitary hormones (i.e., indicators of radiation-associated pituitary damage), such as adult height and reproductive characteristics.

Furthermore, we examined determinants of response to a questionnaire survey in this specific population of subjects treated decades ago, and mainly in childhood. Determinants to be addressed included demographic characteristics, approach strategy, size of questionnaire and type of consent form. A second methodological issue to be examined was the adequacy of using self-reported information on disease status followed by medical confirmation to study cancer incidence in the period before The Netherlands Cancer Registry became operational.

Structure of this thesis

Chapter 2 presents methods and results of a study of all-cause and cancer-specific mortality in The Netherlands NRI cohort. The first part of Chapter 3 describes a randomized study conducted to assess participation rates for two differently sized questionnaires and two types of consent forms. Based on the results of the randomized study, the main health questionnaire survey was conducted in the full cohort. In the second part of Chapter 3, determinants of response-behavior in the NRI health-questionnaire survey are described, including approach strategy and demographic characteristics.

In Chapter 4 the results of our study on cancer incidence in the NRI-cohort are presented, followed by Chapter 5, a validation study of the assessment of cancer incidence based on self-administered questionnaire data compared to cancer registry linkage. Chapter 6 presents a study on risk of benign disorders in The Netherlands NRI cohort, including benign head and neck tumors, thyroid disorders, indicators of radiation-associated pituitary gland damage and non-melanoma skin tumors. In Chapter 7, the results of the studies described in Chapters 2-6 are discussed and recommendations for further research are given.

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2

Cancer mortality after nasopharyngeal radium irradiation in The Netherlands: a cohort study

Summary

Background: Nasopharyngeal radium irradiation (NRI) was widely used from 1940 through 1970 to treat otitis serosa in children and barotrauma in airmen and submariners. We assessed whether NRI-exposed individuals were at higher risk for cancer-related deaths than non-exposed individuals. Methods: We conducted a retrospective cohort study of all-cause and cancer-related mortality in 5358 NRI-exposed subjects and 5265 frequency-matched non-exposed subjects, who as children were treated at nine Ear, Nose and Throat clinics in The Netherlands from 1945 through 1981. We recorded personal and medical data from original patient medical records and assessed vital status through follow-up at municipal population registries. Risk of mortality was evaluated by standardized mortality ratios (SMRs). All statistical tests were two-sided.
Results: The average radiation doses were 275, 10.9, 1.8, and 1.5 cGy for nasopharynx, pituitary, brain, and thyroid, respectively. The median follow-up was 31.6 years. Three hundred two NRI-exposed subjects had died with 269.2 deaths expected (SMR = 1.1, 95% confidence interval [CI] = 1.0 to 1.3); among non-exposed subjects 315 died with 283.5 expected (SMR = 1.1, 95% CI= 0.99 to 1.2). Cancer-related deaths of 96 exposed subjects (SMR = 1.2, 95% CI = 0.95 to 1.4) and 87 non-exposed subjects (SMR = 1.0, 95% CI = 0.8 to 1.3) were documented. There were no excess deaths from cancers in the head and neck area among exposed subjects. However, there were excess deaths from cancers of lymphoproliferative and hematopoietic origin (SMR = 1.9, 95% CI = 1.1 to 3.0), mainly from non-Hodgkin's lymphoma (SMR = 2.6, 95% CI = 1.0 to 5.3). We found no evidence that breast cancer deaths were less than expected (SMR = 1.7, 95% CI = 0.9 to 2.8) in contrast to an earlier study.
Conclusions: Our findings do not indicate an increased cancer mortality risk in a population exposed to NRI in childhood. More prolonged follow-up of this and other NRI cohorts is recommended.

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Introduction

From the early 1940s until the mid-1960s nasopharyngeal radium irradiation (NRI) was considered to be an effective therapy for childhood Eustachian tube dysfunction (secretory otitis media) [1,2]. In the United States, NRI was also applied to aviators and submariners with middle ear barotrauma [3,4]. Both disorders are characterized by lymphoid tissue hyperplasia in the nasopharynx. NRI therapy involved inserting a radium-containing cylinder through the nostril into the nasopharyngeal cavity, close to the tubal orifice, which effectively shrank the lymphoid tissue in that area [5]. High radiation doses, (i.e., up to several grays), were delivered to the nasopharyngeal cavity, whereas other tissues in the head and neck area, such as the thyroid gland, salivary glands and brain, received low doses of radiation (i.e., <30 cGy) [6]. At least 8000 servicemen and as many as 2.5 million civilians may have been treated with NRI in the United States [7,8]. NRI therapy was also reported in Canada [8] and in several European countries [8,9], including The Netherlands, where at least 24,500 patients were estimated to have been treated [9]. NRI therapy was abolished gradually because it was acknowledged that radium treatment might cause adverse late health effects [10], and new effective forms of therapy for secretory otitis media were introduced.

Several cohort studies Two U. S. [11-13] have addressed the long-term cancer risks in children treated with NRI. In addition, Kang et al. [14] studied mortality among military personnel who were treated with NRI, but such studies [15,16] are difficult to conduct because military medical records are often no longer accessible. Because of the small sample sizes and relatively short follow-up periods in all studies, results regarding NRI-associated cancer risk so far have been inconclusive. However, there has been public concern and scientific controversy over a possible increased risk of brain tumors in NRI-treated individuals [17-19]. A 1995 workshop [20] addressing "the public health response to NRI" resulted in recommendations for additional research into the late health effects among NRI-treated populations, including extending the follow-up period of existing cohorts and paying more attention to cancer end points.

In this report, we present the overall and cause-specific mortality results after a prolonged follow-up of a Dutch cohort of patients treated with NRI. We focused on cancers of the head and neck area and of lymphoproliferative and hematopoietic origin. In addition, because radiation damage to the pituitary gland has been hypothesized to reduce the risk of hormone-dependent cancers [21], we also focused on cancers of hormone-dependent tissues, including the breast, the female genital tract, and the prostate gland.

Subjects and methods

Study population

In 1982, a cohort of 2547 NRI-exposed subjects previously treated with NRI from 1945 through 1965 was identified from patient medical records from the ear, nose, and throat (ENT) departments of five clinics in The Netherlands. A frequency-matched non-exposed subject group of 2381 ENT patients who were not treated with NRI was identified on the basis of clinic, sex, year of birth and year of first consultation. Further details on the original cohort have been described previously [13]. For this study, the cohort was expanded to include additional Dutch subjects who had received NRI treatments from 1945 through 1981. The additional NRI-exposed subjects were identified from medical records of ENT departments in three clinics that had not participated in the previous study [13] and in two clinics that had already participated. NRI-exposed subjects were grouped by sex, date of birth, and date of first radiation treatment (5-year periods). Non-exposed subjects were selected from the patient rosters in the same clinics. To avoid selection bias, all units (i.e., boxes or drawers) of the medical records were assigned a rank number, and tables of random numbers were used to select units that were searched until a matched non-exposed subject was found for each NRI-exposed subject. We added 2845 NRI-exposed subjects and 2920 matched non-exposed subjects to the original cohort for a total of 5392 NRI-exposed subjects and 5301 non-exposed subjects.

For one clinic, we could not find sufficient numbers of records to frequency match NRI-exposed and non-exposed subjects for the expanded search. Therefore, we selected 90 non-exposed subjects from another hospital in the same region. NRI-treated subjects from one of the three new participating clinics were included in the present study by restricting their person-year experience and deaths to the period from 1982 through 1997 since data were incomplete for the earlier years.

Institutional review boards of all participating hospitals and research institutes approved the study protocol, and all living subjects provided written informed consent.

Data collection

Trained research assistants completed a study data form for each cohort member. We recorded personal data, including name, date of birth, sex, and address at the time of treatment. If the date of birth was not given, the year of birth was calculated from the date of the first

consultation and the subject's age at that time. We also recorded medical data, including the date of the first consultation, treatment status (NRI or non-exposed) and initial diagnosis. For NRI-exposed subjects, both the date and the duration of each treatment session were recorded. In addition, we collected information on the standard treatment protocols and characteristics of the radium applicators in every clinic (see below).

Follow-up

An attempt was made to collect complete vital status information for each cohort member from the date of first ENT treatment until the date of death, emigration, or closure to the study (September 15, 1997). For subjects from the original cohort, the vital status as of February 1, 1985 was already available. However, for subjects in the expanded cohort, the vital status had to be retrieved based on the names and (mainly childhood) addresses listed in the medical records. Vital status and current address of cohort members were ascertained through information provided by the municipal population registries. These registries keep highly accurate records of the Dutch population and are, therefore, commonly used for follow-up studies [22].

We sent a letter requesting information on the vital status of each cohort member to the population office of the last known municipality of residence. If a cohort member had died, the date, the place of death, and the death certificate number were recorded. If a cohort member had moved, the inquiry proceeded to the new municipality. This procedure was repeated until the vital status of the cohort member as of September 15, 1997, was confirmed. If a cohort member had emigrated, we contacted a special bureau of the Dutch Ministry of Foreign Affairs that keeps records of persons who move abroad and registers the new place of residence in case they return to The Netherlands. We could not obtain the vital status for a small number of cohort members who were considered lost to follow-up because either they were unknown in the municipality listed on the medical record or they had left their hometown without notifying the municipality. For these cohort members, a final search request was sent to the Central Bureau of Genealogy, a nationwide registry of deceased Dutch citizens, in which records are indexed only by name and year of death.

Information was obtained from Statistics Netherlands on the cause of death for each deceased cohort member. All causes of death in The Netherlands are coded by trained nosologists at Statistics Netherlands who use the International Classification of Diseases [23]

applicable to the particular calendar period. For this study, all registered causes of death that used earlier revisions were re-coded according to the 9th revision.

Among the eligible 5392 NRI-exposed subjects, 34 were excluded because of incomplete NRI treatment data (N=23) or unknown sex or date of birth (N=11). Among the eligible 5301 non-exposed subjects, 36 were excluded because of the uncertainty about treatment status (N=5), duplication in the cohort (N=5), unknown sex or date of birth (N=9), or unknown date of first treatment (N=17). Thus, this study analyzed data from 5358 NRI-exposed subjects and 5265 non-exposed subjects with complete data on all relevant variables. The cohort included 57% males. Eighty percent of cohort members were born from 1940 through 1970. Fifty-two percent of NRI-exposed subjects had their first radiation treatment between the ages of 5 and 9 years, 21% were treated before the age of 5 years, and 11% were treated after the age of 19 years. The median follow-up was 31.6 years.

Dosimetry

An NRI treatment typically consisted of one to four daily sessions, usually separated by intervals of 1 week, depending on the clinic's standard treatment protocol. A session consisted of a single radium source inserted into the nasopharynx for 5-20 minutes. Fewer than 1% of all NRI-exposed subjects received more than one treatment.

For one clinic, sources were placed bilaterally; however, for the other clinics, the source was inserted in either the right or theleft nostril and alternated on subsequent sessions, if any. A standard treatment sequence of right-left-right-left (used in the clinic where the majority of treatments took place) was assumed for NRI-exposed subjects for whom laterality was unknown. Total radium treatment was expressed in total milligram-hours [6] (mgh, the product of mg radium and treatment time in hours, range 3-74 mgh, mean 18.2 mgh). Because measurements of organ doses during the treatments were not available, the absorbed radiation doses to various organs (i.e., head and neck area and breast) had to be calculated on the basis of measurements in anthropomorphic phantoms.

Most applicators contained radium within a Monel filter, a nickel alloy, of 0.1-0.3 mm in thickness. Sources with Monel filters are now obsolete and were not available for testing; however, the dose distribution up to 10 cm from a Monel-filtered source was published by Verduijn [9]. The dose distribution from a platinum-filtered radium source measured in a tissue-equivalent phantom [24] showed that a Monel-filtered source resulted in doses that were approximately 15% higher. The Monel dose distribution was used to estimate dose to organs up

to 10 cm from the source; at greater distances, the organ doses were estimated by increasing the absorbed dose from a platinum-filtered source by 15%. These data were applied to all patients, although the filter material and thickness were known only for the clinics included in the earlier study [9].

Absorbed doses to the organs of interest were calculated by use of the distance from the nasopharynx to each organ for children of various ages [25]. We assumed that the nasopharyngeal cavity was 2.0 cm in diameter, regardless of age, and that the radium applicator was placed in the center of each side of the cavity [9]. To calculate the absorbed dose to the brain, we estimated the radiation for multiple anatomical subsites for each subject. Both the average and the maximum dose to these sub-sites within each individual were treated as representative of the dose to the brain for that subject. Total active bone marrow (ABM) doses were calculated by use of the age-specific proportional distributions of ABM published by Christy [26].

Statistical analysis

Person-years at risk were calculated from the date of first NRI treatment for NRI-exposed subjects or the date of first consultation for non-exposed subjects, until the date of death, emigration, loss to follow-up, or end of follow-up (September 15, 1997). For a subgroup of 237 NRI-exposed subjects at one specific clinic (see "Study population"), the date of entry in the study was fixed at January 1, 1982.

For comparison with the Dutch general population, the numbers of deaths observed (O) in both the NRI-exposed and non-exposed subject groups were compared with the numbers of deaths expected (E). To calculate the expected numbers of deaths, person-years were multiplied by the appropriate sex-, age- and calendar period-specific reference death rates from 1950 through 1997 for the general population (Department of Population, Statistics Netherlands) and summed. Data were stratified by calendar period of follow-up (1940-1949, 1950-1959, 1960-1969, 1970-1979, 1980-1989, 1990-1997), sex, attained age (0-4, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and ≥80 years), treatment prescription dose (non-exposed, <10, 10-19, 20-29, 30-39, and ≥40 mgh), age at first treatment (0-4, 5-9, 10-14, 15-19, 20-29,30-39,40-49, and ≥50 years) and clinic. For each cell of the aggregated data file, the number of person-years and the number of observed and expected deaths were calculated. In addition, the number of person-year weighted averages of attained age, age at first treatment, and organ-specific radiation doses were calculated.

Standardized mortality ratios (SMR, defined as the O/E ratio) were obtained, and likelihood-ratio based 95% confidence intervals (CI) were calculated under Poisson assumptions for the observed frequencies [27,28]. SMR analyses were performed for all-cause mortality, major disease categories, and cancer-specific mortality, particularly for cancers of the head and neck area, breast, female genital tract and prostate and for malignancies of hematopoietic and lymphoproliferative origin. Among NRI-exposed subjects, analyses were stratified by follow-up period, age at first treatment, and treatment prescription dose for selected tumor sites. Trend tests for SMR were performed as described by Breslow and Day [28].

Relative risk (RR) analyses used Poisson regression with cell-specific observed values and cell-specific expected frequency instead of person-years [29]. That is, for each cell, the observed frequency was assumed to correspond to a Poisson variable, with a mean equal to the expected frequency of the population (E), treated as known, times a parametric function that depended on exposure or estimated radiation dose (D). Thus, the model for comparing non-exposed subjects and NRI-exposed subjects was mean (O) = αE for non-exposed subjects and $\alpha E(1+\beta)$ for NRI-exposed subjects, where α and β are unknown parameters, RR = $1+\beta$, and the excess RR (ERR) = β. For radiation dose-specific comparisons, the linear model is mean (O) = $\alpha E(1+\gamma D)$, where γD = the ERR at dose D and the unknown parameter γ = ERR per unit dose. Finally, a general model was used in which an effect of exposure per se was combined with a linear dose response among the exposed: mean (O) = $\alpha E(1+\beta e)(1+\gamma D)$ where e is an indicator for NRI treatment. All statistical tests were two-sided.

Results

Mortality was compared between NRI-exposed and non-exposed subjects in a Dutch cohort of patients. In all, tracing was completed for 92% of the cohort, regardless of exposure status. Death certificates were available for all but two deceased subjects. The median attained age of those alive in 1997 was 41 years (range, 18-87 years).

Estimates of absorbed doses for several organs associated with NRI are listed in Table 2.1. Tissues in close vicinity of the radium capsule during treatment received substantial radiation doses ranging from 32 cGy to greater than 1000 cGy. The estimated average radiation doses to other organs of interest in the head and neck area were less than 20 cGy, although in 12% of the NRI-exposed subjects, the dose to the pituitary gland exceeded this level. The estimated maximum dose to the brain was greater than 20 cGy in 8% of NRI-exposed subjects; however, estimated the average dose to the brain was less than 10 cGy in all of the NRI-exposed subjects.

Table 2.1
Overview of estimated organ doses in The Netherlands nasopharyngeal radium irradiation cohort

	Dose, cGy		
Organ	Mean	Minimum	Maximum
Nasopharynx	275	32	1,110
Base of tongue	20.7	2	130
Pituitary	10.9	1	59
Parotid gland	7.0	1	28
Brain, maximum*	9.1	1	37
Brain, average†	1.8	0.3	8
Thyroid	1.5	0.2	11
Total ABM‡	0.4	0	3
Breast	0.1	0	0.9

* Maximum dose to 282 points throughout the brain
† Average dose to 282 points throughout the brain
‡ ABM = active bone marrow

The radiation dose to the thyroid was less than 5 cGy in 96% of the NRI-exposed subjects. The estimated average dose to the female breast was 0.1 cGy but was less than 1 cGy in even the most heavily exposed subjects.

The number of deaths in each disease category is shown in Table 2.2. We observed a total of 617 deaths in the cohort treated in ENT-clinics 16-49 years earlier. A total of 302 NRI-exposed subjects had died from all causes in the 158,159 person-years of follow-up, with an SMR = 1.1 (95% CI = 1.0 to 1.3). The most common specific causes of death for NRI-exposed subjects were malignant diseases (O = 96 deaths, SMR = 1.2, 95% CI = 0.95 to 1.4) and disorders of the circulatory system (O = 87 deaths, SMR = 1.1, 95% CI = 0.9 to 1.4). None of the SMRs among NRI-exposed subjects were statistically significant (Table 2.2). A total of 315 non-exposed subjects had died from all causes (SMR = 1.1, 95% CI = 0.99 to 1.2). The most common specific causes of death were malignant diseases (O = 87 deaths, SMR = 1.0, 95% CI = 0.8 to 1.3) and disorders of the circulatory system (O = 73 deaths, SMR = 0.9, 95% CI = 0.7 to 1.2). The SMRs for disorders of the central nervous system (SMR = 2.1, 95% CI = 1.2 to 3.5) and the respiratory system (SMR = 2.3, 95% CI = 1.5 to 3.3) were statistically significant. Although the SMRs were elevated for congenital abnormalities (SMR = 1.8, 95% CI = 0.8 to 3.5) and for disorders of the endocrine and metabolic system (SMR = 1.8, 95% CI = 0.98 to 3.0), the increases were not statistically significant. For all other disease categories, the number of deaths observed was not more than expected or the comparisons were based on very small numbers of deaths.

Table 2.2
Mortality from major diseases in The Netherlands nasopharyngeal radium irradiation (NRI) cohort, by exposure status

Cause of death	ICD-9*	NRI-exposed subjects (158 159 PY)†			Non-exposed subjects (163 756 PY)		
		O	E	SMR (95% CI)	O	E	SMR (95% CI)
All causes		302	269.2	1.1 (1.0 to 1.3)	315	283.5	1.1 (0.99 to 1.2)
Malignant disease	140-208	96	82.2	1.2 (0.95 to 1.4)	87	86.0	1.0 (0.8 to 1.3)
Endocrine, metabolic, & immune systems	240-279	7	7.6	0.9 (0.4 to 1.9)	14	7.8	1.8 (0.98 to 3.0)
Central nervous system	320-349	4	7.0	0.6 (0.2 to 1.5)	16	7.5	**2.1 (1.2 to 3.5)**
Circulatory system	390-459	87	77.0	1.1 (0.9 to 1.4)	73	80.1	0.9 (0.7 to 1.2)
Respiratory system	460-519	12	11.5	1.0 (0.5 to 1.8)	28	12.3	2.3 (1.5 to 3.3)
Digestive system	520-579	14	8.6	1.6 (0.9 to 2.7)	12	9.1	1.3 (0.7 to 2.3)
Congenital abnormalities	740-759	2	3.4	0.6 (0.07 to 2.2)	8	4.5	1.8 (0.8 to 3.5)

* International Classification of Diseases, 9th revision [23]
† PY = person-years; O = observed number of deaths, E = expected number of deaths; SMR = standardized mortality ratio, defined as O/E ; CI = confidence interval.

Table 2.3
Cancer-specific mortality in The Netherlands nasopharyngeal radium irradiation (NRI) cohort, by exposure status

Cancer-specific cause of death	NRI-exposed group (158 159 PY)*		Non-exposed group (163 756 PY)*		RR (radium)
	O	SMR (95% CI)†	O	SMR (95% CI)†	RR (95% CI) †
Head and neck area ‡	5	0.9 (0.3 to 2.2)	7	1.3 (0.5 to 2.6)	0.7 (0.2 to 2.3)
Brain§	2	0.6 (0.1 to 2.1)	5	1.4 (0.5 to 3.2)	0.4 (0.1 to 1.9)
Thyroid	0	(0.0 to 17.2)	0	(0.0 to 16.8)	-
Oral cavity and pharynx	2	1.8 (0.2 to 6.4)	0	(0.0 to 3.4)	-
Larynx	1	1.8 (0.1 to 10.1)	2	3.6 (0.4 to 12.9)	0.5 (0.02 to 5.3)
Lymphoproliferative & hematopoietic	17	1.9 (1.1 to 3.0)	6	0.6 (0.2 to 1.4)	3.0 (1.2 to 8.3)
Non-Hodgkin's lymphoma	7	2.6 (1.0 to 5.3)	2	0.7 (0.1 to 2.6)	3.6 (0.9 to 24.4)
Hodgkin's disease	0	(0.0 to 3.4)	0	(0.0 to 3.4)	-
Multiple myeloma	3	2.8 (0.6 to 8.1)	0	(0.0 to 3.4)	-
Leukemia‖	7	1.6 (0.7 to 3.4)	4	0.9 (0.2 to 2.3)	1.9 (0.6 to 7.2)
Breast	13	1.7 (0.9 to 2.8)	9	1.1 (0.5 to 2.0)	1.6 (0.7 to 3.8)
Female genital tract¶	4	1.1 (0.3 to 2.8)	6	1.4 (0.5 to 3.1)	0.8 (0.2 to 2.7)
Prostate	1	0.4 (0.01 to 2.2)	1	0.4 (0.01 to 2.2)	1.0 (0.04 to 25.0)

* Total number of person-years (PY). The number of PYs among NRI-treated females = 68 213; among non-NRI-treated females = 72 179.
† SMR = Standardized Mortality Ratio, defined as O/E ; O = observed number of deaths, E = expected number of deaths; CI = Confidence Interval; RR = Relative Risk
‡ Defined as International Classification of Diseases, 9th Revision (ICD-9) codes 140-149, 160,161,191 and 193.
§ In addition, two deaths due to brain tumors of non-specified behavior (ICD-9 code 239.6) were observed among exposed subjects, i.e., tumors that could not be defined 'benign' or 'malignant' because of a lack of diagnostic information; adding O and E to the brain tumor analyses rendered a combined SMR of 1.0.
‖ Subtypes of leukemia (number) - among exposed: acute lymphoblastic (one), chronic lymphoblastic (one), acute myelocytic (one), chronic myelocytic (two), subacute myelocytic (one) and unspecified (one); among non-exposed: acute myelocytic (one), acute erythrocyte (one), acute monocyte (one) and acute not otherwise specified (one).
¶ Specific cancer sites (number) - among NRI-exposed subjects: cervix (one), uterus (one), and ovary (two); among non-exposed subjects: cervix (three), uterus (one) and ovary (two).

We next analyzed the data according to specific cancer sites. Five NRI-exposed subjects died from malignant cancers of the head and neck area (SMR = 0.9, 95% CI = 0.3 to 2.2) and seven non-exposed subjects died of such cancers (SMR = 1.3, 95% CI = 0.5 to 2.6) (Table 2.3). Two additional NRI-exposed subjects died from brain tumors that could not be classified as benign or malignant because of a lack of diagnostic information. All NRI-exposed subjects who died of cancers in the head and neck area had been treated with NRI after the age of 40 years, and two deaths occurred within 10 years of NRI treatment. No deaths from thyroid cancer were noted.

We noted more deaths from malignancies of lymphoproliferative and hematopoietic origin than expected (O = 17 deaths, SMR = 1.9, 95% CI = 1.1 to 3.0) among NRI-exposed subjects (Table 2.3). This increase mainly reflected seven deaths from non-Hodgkin's lymphoma (NHL) (SMR = 2.6, 95% CI = 1.0 to 5.3). Also, there were three deaths from multiple myeloma (SMR = 2.8, 95% CI 0.6 to 8.1) and seven deaths from leukemia (SMR = 1.6, 95% CI = 0.7 to 3.4). Among non-exposed subjects, slightly fewer deaths from malignancies of lymphoproliferative and hematopoietic origin were observed than expected (O = six deaths, SMR = 0.6, 95% CI = 0.2 to 1.4). Compared with non-exposed subjects, the RR for NRI-exposed subjects was 3.0 (95% CI = 1.3 to 8.3) for malignancies of lymphoproliferative and hematopoietic origin (Table 2.3). A dose-response analysis, which included the non-exposed subjects, showed a statistically significant effect of ABM dose (ERR/cGy = 4.5, 95% CI 0.5 to 16.9). However, after adjustment for the effect of exposure per se, a dose response relationship could no longer be demonstrated.

Among hormone-related cancers potentially associated with pituitary radiation dose (21), there were more breast cancer deaths than expected (O = 13, SMR = 1.7, 95% CI = 0.9 to 2.8, in 68,213 woman-years of follow-up). No statistically significant association was found between breast cancer mortality and dose to the breast (ERR/cGy = 7.2, 95% CI = -0.9 to 27.4) or to the pituitary (ERR/cGy = 0.07, 95% CI = (-0.009 to 0.28) (data not shown). The number of deaths from cancers of the female genital tract was small (O = 4, SMR = 1.1, 95% CI 0.3 to 2.8) and close to the expected number of deaths (Table 2.3). Only two prostate cancer deaths (one exposed and one non-exposed subject) were observed among males.

We also assessed the possible effects of treatment prescription dose, age at treatment, and time since treatment on the SMR among NRI-exposed subjects (Table 2.4). For malignancies of lymphoproliferative and hematopoietic origin, SMRs were increased for all treatment dose categories, except one (10-19 mgh), and were increased regardless of age at treatment, although not statistically significantly (Table 2.4). When the data were analyzed by time since treatment, there was a statistically significant trend (P=.02) towards increasing SMR with longer follow-up, with SMRs of 2.7 (95% CI = 1.0 to 5.9) and 3.1 (95% CI = 1.4 to 6.2) in

Table 2.4
Mortality from selected cancers in radium-treated subjects of The Netherlands nasopharyngeal radium irradiation cohort, by treatment prescription dose, age at treatment, and time since treatment

Stratification factor	Person-years	All cancers		Cancers of lymphoproliferative and hematopoietic origin		Breast cancer	
	At risk	O*	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)
Treatment prescription dose, mgh†							
<10	7 560	5	1.2 (0.4 to 2.9)	1	2.2 (0.1 to 12.4)	0	(0.0 to 8.2)
10-19	103 545	24	0.9 (0.5 to 1.3)	4	0.9 (0.3 to 2.4)	4	1.3 (0.4 to 3.4)
20-29	17 224	42	1.3 (0.96 to 1.8)	5	2.1 (0.7 to 4.8)	3	1.3 (0.3 to 3.9)
30-39	16 661	15	1.3 (0.7 to 2.1)	5	4.2 (1.4 to 9.7)	4	2.7 (0.7 to 6.9)
≥40	13 167	10	1.5 (0.7 to 2.7)	2	2.6 (0.3 to 9.4)	2	3.2 (0.4 to 11.5)
Age at treatment, y							
0-9	115 538	17	0.9 (0.5 to 1.5)	5	1.2 (0.4 to 2.9)	6	2.5 (0.9 to 5.4)
10-19	27 143	10	0.9 (0.4 to 1.6)	5	3.6 (1.2 to 8.3)	3	1.6 (0.3 to 4.8)
≥20	15 475	69	1.3 (1.0 to 1.7)	7	1.9 (0.8 to 2.9)	4	1.1 (0.3 to 2.9)
Time since treatment, y							
0-9	49 762	10	1.0 (0.5 to 1.9)	1	0.5 (0.1 to 2.7)	0	(0.0 to 5.9)
10-19	47 972	14	0.8 (0.4 to 1.4)	2	0.9 (0.1 to 3.1)	1	0.8 (0.04 to 4.6)
20-29	36 653	31	1.4 (0.96 to 2.0)	6	2.7 (1.0 to 5.9)	3	1.5 (0.3 to 4.2)
≥30	23 771	41	1.2 (0.9 to 1.7)	8	3.1 (1.4 to 6.2)‡	9	2.3 (1.0 to 4.3)

* O = observed number of deaths; SMR = Standardized mortality ratio, defined as O/E; where E = expected number of deaths; CI = confidence interval.
† mgh = activity of radium source in milligrams (mg) x total duration of radiation treatment sessions in hours (h).
‡ P_{trend} =0.02

the intervals of 20-29 years and more than 30 years since treatment, respectively. Female subjects exposed to more than 30 mgh had nonstatistically significantly elevated SMRs. Mortality from breast cancer was negatively, but nonstatistically significantly, associated with age at treatment, with the highest risk found among women treated with radium before 10 years of age. There was a slight, but nonstatistically significant trend (P=.15) between the risk of breast cancer death and increasing time since treatment. Women who were followed for 30 years or more had an SMR = 2.3 (95% CI = 1.0 to 4.3).

Discussion

In this the largest cohort study of NRI-treated subjects to date, we found no association between NRI and subsequent mortality from cancers of the head and neck area, the brain, and the thyroid. Nasopharyngeal tissues adjacent to the radium capsule during treatment were exposed to the highest radiation doses. However, we and others [11,21] found no association between NRI and pharyngeal cancers. Hazen et al. [11] reported no pharyngeal cancers after 15 years of follow-up in 417 NRI-treated subjects and, although Sandler et al. [12] reported one pharyngeal cancer, an anaplastic soft palate cancer, in 904 NRI-treated subjects, prolonged follow-up of this cohort revealed no additional pharyngeal cancers [21]. It has been suggested that the local radiation dose in the nasopharyngeal cavity may have been sufficiently high up to 11 Gy in our study) to induce cell death, which would preclude the generation of any malignancy [30].

We found no deaths from thyroid cancer perhaps because the extremely low dose of radiation to the thyroid (mean, 1.5 cGy) was not sufficient to induce an observable number of tumors. Alternatively, our study may have insufficient statistical power to detect such an association [31,32], because few fatal thyroid malignancies were expected (<1). Excess thyroid cancer risk has been described after exposure to doses as low as 10 cGy [33].

We found no more deaths from brain cancer than expected. Yeh et al. [21] reported a statistically non-significant RR of 14.8 (95% CI = 0.8 to 286.3) for brain cancers on the basis of three deaths in their cohort and noted four benign brain tumors. However, the average radiation dose to the pituitary in their study [21] was estimated to be at least 78 cGy, which was much higher than the 11 cGy in our study. In the New York NRI cohort [11], only one brain cancer was observed among NRI-exposed subjects compared with two among non-exposed subjects. A follow-up study of 1,214 NRI-treated and 3,176 untreated adult submarine trainees during World War II [14] reported slightly elevated mortality from head and neck cancers as a group (RR = 1.4, 95% CI = 0.5 to 3.5), without further detail. Thus, evidence regarding brain cancer risk following NRI treatment is mixed and no definitive conclusions can be reached.

High-dose childhood radiation exposures in the head and neck area have been linked to elevated brain cancer risk [34,35]. A study among 28,008 infants treated for skin hemangioma [36] reported an excess risk associated with radiation doses partly overlapping those experienced by subjects in our NRI cohort. The excess risk was inversely associated with the age at treatment, with the highest risk among those treated before the age of 5 months. Because the average age at treatment in our study was higher and the average dose to the brain was lower, the two studies are not necessarily inconsistent.

We noted more deaths from malignancies of lymphoproliferative and hematopoietic origin, which became evident more than 15 years after NRI treatment and mainly reflected an increase in the risk of fatal NHL. Elevated risks for NHL or multiple myeloma were not reported in the U. S. NRI cohorts [11,21] or in studies of other types of childhood radiation treatments to the head and neck area [37-39]. If any, the effect of low-dose radiation in the etiology of NHL and multiple myeloma is thought to be small or nonexistent [40,41]. Thus, the possibility of a chance finding should also not be ruled out, since numbers were small and multiple statistical testing was done. Furthermore, with regard to a possible dose-response relationship, our data were statistically just as consistent with an effect of exposure per se as with a linear effect of dose. In NRI treatment, lymphoid tissues in the nasopharynx receive substantial doses of radiation. Unfortunately, the available data on death certificates precluded our analysis of NHL site-specific mortality.

Leukemia has been associated with radiation exposure [40]. Increased risk of death from leukemia could be detected among atomic bomb survivors exposed to greater than 20 cGy (total ABM dose) [42] and among young adults exposed to head and neck irradiation for tinea capitis during childhood [37]. In both of the studies [37,42], the peak incidences of leukemia were reached within 10 years after radiation exposure. The total ABM dose in our study was only 0.4 cGy, and the slight increased risk was not observed until 20 years after the NRI treatment. Consequently, it is questionable if our elevated SMRs for malignancies of hematopoietic and lymphoproliferative origin are due to radiation.

Yeh et al. [21] reported a decreased risk for a combined group of hormone-related cancers (breast, ovarian, endometrial, and prostate cancer) in a cohort of 914 NRI-exposed subjects and hypothesized a possible association between the NRI radiation dose and the pituitary. In our study, no evidence of decreased mortality from breast or female genital tract cancers was found. If at all, cancer-specific mortality appeared to increase with increasing doses of radiation to the pituitary. One out of many possible explanations for the discrepancy between

our results and those of the Maryland cohort [21] might be that the average radiation dose to the pituitary in the latter study was much higher than that in our cohort.

The strengths of our study design are as follows: Data on individual radiation treatments were verified, and a fair range of radiation exposures was established. We also identified an internal reference group to ensure unbiased comparisons because ENT patients might have a different pattern of disease occurrence than the general population. Analyses revealed, however, that non-exposed subjects had increased mortality from respiratory diseases and central nervous system disorders. These patterns may be related to the diagnosis at first consultation at the ENT clinic because the majority of NRI-exposed subjects (92%) were referred with recurrent (serous) otitis compared with only 36% of non-exposed subjects. By contrast, almost 20% of the non-exposed subjects were referred for diverse reasons, representing a wide variety of ENT symptoms related to systemic disorders with complications in the ENT area compared with fewer than 1% of the exposed subjects. Because the median attained age of the cohort was only just above 40 years, the expected numbers of site-specific cancer deaths were generally small. The statistical power of our study was sufficient to detect a 2.5-fold increase in the risk of death from a cancer of the head and neck area with 80% probability [28].

In summary, this report on a Dutch cohort of NRI-treated patients did not reveal strongly increased risks for mortality from cancer. Our analysis of cancer incidence in this cohort is underway, which should provide a more thorough evaluation for cancers with good prognosis and for the incorporation of confounding factors in the analysis. Within 10-15 years from now, the majority of the NRI-exposed subjects will be between 40 and 60 years of age and, the underlying risk of cancer will rise substantially in accord with the risk of cancer for the general population. More specific analyses of the patterns of cancer-specific deaths will then be feasible. Any definitive conclusions regarding the risk of cancer associated with NRI must await further prolonged follow-up.

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3

Response-behavior in a mailed health questionnaire survey as part of a retrospective cohort study

Summary

As part of a Dutch retrospective cohort study of adult subjects treated for ear, nose, and throat conditions in childhood, we examined the effect of questionnaire length and type of consent form on participation rates in a self-administered questionnaire survey. Despite widespread use of questionnaires in observational research, few randomized studies of questionnaire methods have been conducted. We examined 200 individuals, randomly assigned to one of four categories, divided by length of questionnaire (long vs. short) and type of consent form (basic vs. multi-option). A ten percent difference in participation rate by questionnaire length (statistically non-significant) but no heterogeneity by type of consent form was demonstrated. Furthermore, we report on approach procedures and study population characteristics in relation to response behavior. The eligible cohort consisted of 8,402 subjects, with an average age at questionnaire completion of 41 years (range, 18-87 years). Two mailings and a telephone survey were used. The written reminder added 15 percentage points and the telephone survey another 10 percentage points to the ultimate participation rate of 74 percent. Of the population characteristics studied, attained age, sex, exposure status, age at exposure, and having participated in a former follow-up survey were important determinants of participation rates. Male nonparticipants were more likely to not respond rather than to refuse, whereas a trend of increasing refusal rates, but not non-response rates, with advancing age at questionnaire completion was demonstrated. In summary, questionnaire length, but not type of consent form, as well as attained age, sex, exposure status, age at exposure and having participated in a former follow-up study affected participation rates.

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Introduction

Self-administered mailed questionnaires are widely used in observational studies and there is a large number of reports describing participation rates, with a wide variety of study designs, goals, exposures, outcomes of interest and study population characteristics [1-6]. Nevertheless, the first randomized studies on the effectiveness of questionnaire surveys in terms of participation rates and determinants of response were only recently published [6,7]. As part of a Dutch retrospective cohort study among adult subjects treated for ear, nose, and throat (ENT) conditions in childhood, we planned a mailed health questionnaire survey. The majority of patients were treated before reaching 10 years of age, and time since first treatment was more than 40 years for some individuals. Therefore, we were concerned that a number of patients might not be aware of any treatments in the past and as such, would be less motivated to participate in the study. Privacy-related aspects of the study, such as necessary record linkage procedures, added to this concern. We considered adequate patient information, questionnaire length and type of consent form to be potentially influential factors in determining the participation rate.

Using a randomized design, we examined the effect of questionnaire length and type of consent form on the participation rates in a health questionnaire survey. We also examined the effects on participation rates of different approach procedures and various study population characteristics.

Materials and methods

Study population

We studied a nationwide cohort of patients who had been treated for ENT conditions from 1945 through 1981, in the ENT departments of nine clinics in The Netherlands, to study possible late health effects of nasopharyngeal radium irradiation (NRI). We identified 5,358 eligible patients ever treated with NRI and a frequency-matched (clinic, sex, birth & first treatment year) non-exposed group of 5,265 subjects who had also been treated for ENT conditions, but had never been exposed to NRI. Part of the cohort had already received a questionnaire in 1985 [8,9]. Institutional review boards of all participating hospitals and research institutes approved the study protocol.

The median age at treatment was 6 years and the median follow-up time was 30 years. Main outcomes of interest included cancer-specific mortality, cancer incidence, and a history of benign disorders possibly related to radiation exposure of the pituitary and thyroid glands. Further details have been reported elsewhere [10,11].

Randomized study on effectiveness of questionnaire length and type of consent form

In the spring of 1997, we conducted a randomized study to test the effectiveness of the questionnaire and the informed consent form in attaining high participation rates. We developed an 8-page, 33-item questionnaire (the so-called "short questionnaire") that provided sufficient information on basic characteristics, health status and exposure to carcinogens other than NRI. The short questionnaire was compared to a "long", 12-page, 54-item version, with additional questions on female reproductive history, occupational exposures and diet.

In addition, two different types of consent forms were developed. The basic consent form consisted of a standard declaration, providing a brief, but informative overview of the purpose of the study, the study procedures and several privacy considerations. The participant's signature and date at the bottom of the basic form served as proof of informed consent for every procedure mentioned in the declaration. The alternative version, a so-called "multi-option consent form", consisted of the exact same description of study purpose, study procedures and privacy considerations. However, instead of the single signature authorization procedure described above, the multi-option form ended with a listing of the three study procedures requiring informed consent and for each of them check-boxes indicating "yes" (i.e., consent) or "no" (i.e., objection). The multi-option form also had to be signed and dated. The three study procedures requiring individual informed consent were (1) retrieval of medical data from ENT files, (2) retrospective and prospective linkage with The Netherlands Cancer Registry and (3) keeping study files for 20 years at the coordinating research center.

In general, only hospital administrations and treating physicians are allowed to register both personal and medical data in one patient record. For future research we preferred not to depend on hospital medical files but, rather, to create a study database with all relevant information. We were concerned that old patient records might be destroyed in the near future, owing to new Dutch privacy laws in medicine [12]. Consequently, we needed individual consent to keep personal and medical data at the coordinating study center to ensure availability of the cohort for future follow-up.

For the randomized study, a random sample of 200 subjects was drawn from the cohort. The sampling frame was limited to the subjects treated in the one clinic situated near the coordinating research center, which contributed 6,932 (65%) of the total number of 10,683 cohort members. Since follow-up had not yet been completed, the sampling frame was further restricted to those subjects alive and with known addresses as of March 1, 1997 (n = 4,180). A 2 x 2 between-groups design was applied, crossing questionnaire length with type of consent form [13]. A ranking number was assigned to all subjects in the sampling frame. To include 200 subjects, we randomly chose a rank among the first 400 numbers as starting point and from there every twentieth subject was sequentially allocated to one of four sections until each group contained 50 subjects (Table 3.1). Group 1 received the short questionnaire and the basic consent form, group 2 received the long questionnaire and the basic consent form, group 3 received the short questionnaire and the multi-option consent form and group 4 received the long questionnaire and the multi-option consent form.

The approach strategy consisted of a first mailing and a written reminder after four weeks in case of non-response (i.e., no participation and no refusal). According to Dutch privacy law [14], invitation letters were printed on hospital stationary and signed by the collaborating ENT-physician in the clinic where the cohort members had been treated in the past. Both mailings consisted of the personal study invitation letter, a questionnaire and a consent form according to subgroup status, and a pre-paid return envelope. The invitation letter explained the purpose of the study "to assess long-term health status among patients who have been treated in ear-nose-throat clinics in the past", and it included a listing of ENT treatments. Exposure status was not revealed, i.e., exposed and non-exposed subjects received personal invitation letters of identical content. For subjects who chose not to participate in the study and who preferred not to be contacted again, the invitation letter and the reminder letter contained clear instructions to return the blank consent form.

Table 3.1
Allocation of subjects to subgroups in the randomized study to assess participation rates according to questionnaire length and type of consent form, as part of The Netherlands NRI cohort study

	Questionnaire		
Consent Form	Short	Long	Overall
Basic	50	50	100
Multi-option	50	50	100
Overall	100	100	200

The reminder letter also mentioned the possibility of a telephone contact in case of no response.

Within four to eight weeks after the second mailing, a determined effort was made to contact non-responders by telephone. Subjects who could not be reached were called at different times of a day and at different days of the week (including Saturdays) and at least 10 attempts for contact were made. As a final step, we planned home visits for all non-responding subjects who had not been reached by phone, i.e., subjects with non-listed telephone numbers, subjects without telephone connections, and subjects with known telephone numbers who were never reached during the telephone survey. Prior to the planned date of the actual visit, a pre-notification letter was sent out, offering the explicit possibility of refusal. If the refusal note was not returned within 10 days, three attempts were made for a home visit.

Questionnaire survey in full cohort

The NRI questionnaire survey of the full cohort was conducted between September 1997 and January 1998. A final questionnaire (8 pages, 43 items) and informed consent form (basic type) were constructed after completion of both the randomized study and the follow-up procedures for the entire cohort. The approach strategy was analogous to that in the randomized study, except that no home visits were carried out in the full cohort survey.

Analytic cohort

Vital status as of September 15, 1997 remained unknown for 864 subjects (8 percent) and 617 (6 percent) subjects had died, leaving 9,142 (86 percent) subjects known to be alive and residing in The Netherlands. For the present analyses, we excluded 740 subjects for the following reasons: (a) Four smaller clinics (N=475 subjects) were not involved in the telephone survey; (b) a subgroup of non-responders (N=255) to the first mailing was not contacted any further as they received the first mailing questionnaire in the last survey month, because they moved houses between our follow-up and survey procedures and (c) 10 subjects were not contacted at all according to their preference expressed in the 1985-survey. Thus, 8,402 subjects remained eligible for analysis of determinants of participation rates, including the randomized study subsample.

Statistical methods

A χ^2 test was used to test for differences in participation rates in the randomized trial [15]. A multivariate logistic regression analysis was performed to quantify the association of each of the selected variables with the participation rate, adjusting for the effects of other variables. Likelihood ratio tests were used to test different nested models against one another [16].

Results

Randomized study on effectiveness of questionnaire length and type of consent form

Effectiveness of the randomization procedure was tested by comparing age-, sex- and exposure category distributions among the four groups. In the random sample as a whole (n=200) the average age at the time the questionnaire was sent was 40 years, 60 percent were male, and 50 percent were exposed. These characteristics were equally distributed over the four subgroups and also in agreement with the entire cohort (not shown).

In all, 144 out of 200 questionnaires were completed, corresponding to an overall participation rate of 72 percent (Table 3.2). Stratification by questionnaire length revealed a statistically non-significant ($p = 0.12$) difference of 10 percentage points between the short questionnaire group (77 percent) and the long questionnaire group (67 percent). The refusal rates were comparable, implying that the difference arose from true non-response (7 percent in the short vs. 15 percent in the long questionnaire group). The participation rates by type of

Table 3.2
Participation rates (%) by type of questionnaire and consent form. A randomized study in The Netherlands NRI cohort study

	Questionnaire		
Consent Form	Short	Long	Overall
Basic	78	68	73
Multi-option	76	66	71
Overall	77	67*	72

* difference by questionnaire length 10% (95% CI = -2% to 22%)

Table 3.3
Contribution of subsequent approach procedures to the participation rate and the refusal rate in The Netherlands NRI questionnaire survey

	Participants		Refusal	
Study procedure	No.	%	No.	%†
Mailing 1	4,144	49	273	3
Mailing 2	1,258	15	521	6
Telephone survey	842	10	446	5
Total*	6,235	74	1,246	15

* total participation rate includes 6 subjects who participated after a home visit in the randomized study
† percentages do not add up to total refusal rate due to rounding

consent form were comparable, but the refusal rate was slightly higher among subjects who received the multi-option consent form (20 percent) compared to the basic form (14 percent). Of 71 participants in the multi-option consent subgroup, 65 gave full consent and three partial consent, i.e., permitted for two out of three study procedures. The other three subjects had not completed the form correctly.

Questionnaire survey in full cohort

Of 8,402 eligible subjects, 6,235 (74 percent) completed a questionnaire. Table 3.3 shows the absolute contribution of the subsequent approach procedures to the ultimate participation rate, expressed in percentage points. The majority of participants responded after the first mailing. The written reminder added 15 percentage points to the ultimate participation rate, and the telephone survey among non-responders another 10 percentage points. Since the home visits (which were quite labor intensive) added only two percentage points to the participation rate in the randomized study (not shown), they were omitted in the final questionnaire survey.

The contribution of the telephone survey to the final participation rate was also examined by population characteristics (Table 3.4). The contribution of the telephone survey showed a strong trend with attained age, and was most effective among subjects in their twenties at time of questionnaire completion (adding 13 percentage points), and much less among subjects older than 70 (adding 5 percentage points). Other variables that showed statistically significant variation in effectiveness of the telephone survey were gender and clinic.

Table 3.4
Contribution of mailings and telephone survey to overall participation rates in the Netherlands NRI questionnaire survey, by population characteristics

		Participation rate (%)		
Characteristic	No.	After two mailings	Additional, from telephone survey	Total†
Sex				
Female	3701	68	9	77
Male	4701	61	11	72
p (χ^2 test)		*	*	*
Exposure status				
Non-exposed	4123	60	11	71
Exposed	4279	68	9	77
p (χ^2 test)		*		*
Attained age (yrs)				
<30	1361	61	13	74
30-39	2653	65	11	75
40-59	3806	66	9	75
≥70	132	54	5	59
p (χ^2 test)		*	*	*
Age at treatment (yrs)				
<3	1102	59	12	70
3-4	1602	67	9	76
5-9	3565	66	11	77
10-14	1041	64	10	74
≥15	1092	60	8	68
p (χ^2 test)		*		*
Time since treatment (yrs)				
<25	1863	63	12	74
25-29	1625	64	11	74
30-34	1458	64	10	74
35-39	1684	66	9	75
≥40	1772	65	8	73
p (χ^2 test)				
Included in previous questionnaire survey ?				
No	4516	63	11	74
Yes	3886	66	9	75
p (χ^2 test)				
Clinic‡				
1	5991	64	10	75
2	831	63	15	78
3	1138	67	5	71
4	195	59	8	67
6	247	64	6	70
p (χ^2 test)			*	*

* p (χ^2 test) < 0.001
† percentages do not always add up to total participation rate due to rounding and because participants (N=6) after home visit (as part of the randomized study) are only counted in total participation rate
‡ clinic numbers are not sequential due to exclusion of 4 clinics (see *Methods* section)

Table 3.4 also provides an overview of the total participation rate by potential determinants of response behavior. In crude analyses, the absolute overall participation rate was higher in women vs. men, exposed vs. non-exposed, and younger (<60 yrs) vs. older (≥60 yrs) subjects; exposed females had the highest participation rate (81 percent) and non-exposed males the lowest (69 percent). Subjects treated below 3 and above 15 years of age showed lower overall participation rates than the remainder. However, the majority of subjects who were older than 15 years of age at treatment were also in the highest category of age in 1997 (> 69 yrs) and might have had lower participation rates associated with attained age. Time since treatment did not influence the participation rate, whereas variability was seen by clinic. The crude analysis did not reveal heterogeneity in participation rates with regard to inclusion in the previous questionnaire survey or not. We then assessed whether there were differences between the subgroups of participants, non- responders and refusers with regard to population characteristics (Table 3.5). Males and individuals who were less than 30 years of age at questionnaire completion were slightly over- represented in the group of non-responders, whereas the subjects over 60 years of age were over-represented in the group of refusers. Furthermore, individuals who had not been included in the 1985 questionnaire survey (i.e., were in the new part of the cohort) were slightly over- represented in the group of non-responders.

Table 3.5
Description of three questionnaire response subgroups in terms of cohort characteristics

Characteristic	Questionnaire response subgroups†					
	Participants		Non-responders		Refusers	
	No.	%	No.	%	No.	%
Sex						
Female	2854	46	322	35	525	42
Male	3381	54	599	65	721	58
Exposure status						
Non-exposed	2936	47	496	54	691	55
Exposed	3299	53	425	46	555	45
Attained age (yrs)						
<30	1010	16	215	23	136	11
30-39	2001	32	301	33	351	28
40-59	2848	46	362	39	596	48
60-69	231	4	25	3	82	7
≥70	145	2	18	2	81	7
Age at treatment (yrs)						
<3	775	12	168	18	159	13
3-4	1224	20	182	20	196	16
5-9	2730	44	381	41	454	36
10-14	766	12	103	11	172	14
≥15	740	12	87	9	265	21
Included in previous questionnaire survey ?						
No	3320	53	544	59	652	52
Yes	2915	47	377	41	594	48
Clinic‡						
1	4471	72	687	75	833	67
2	649	10	63	7	119	10
3	812	13	116	13	210	17
4	131	2	29	3	35	3
6	172	3	26	3	49	4

† due to rounding percentages do not always add up to 100%
‡ clinic numbers are not sequential due to exclusion of 4 clinics (see *Methods* section)

Table 3.6
Multivariate analysis of cohort characteristics associated with the overall participation rate in The Netherlands NRI questionnaire survey

Characteristic	OR of participation* (95% CI)†
Sex	
Female	1.0‡
Male	0.8 (0.7 to 0.8)
Exposure status	
Non-exposed	1.0‡
Exposed	1.3 (1.2 to 1.5)
Attained age (yrs)	
<30	1.0‡
30-39	1.0 (0.9 to 1.2)
40-59	1.0 (0.8 to 1.2)
60-69	0.9 (0.6 to 1.3)
≥70	0.6 (0.4 to 0.9)
Age at treatment (yrs)	
<3	1.0‡
3-4	1.3 (1.1 to 1.5)
5-9	1.2 (1.1 to 1.5)
10-14	1.1 (0.9 to 1.3)
≥15	1.0 (0.8 to 1.3)
Included in previous questionnaire survey ?	
No	1.0‡
Yes	1.2 (1.0 to 1.4)
Clinic¶	
1	1.0‡
2	1.1 (0.9 to 1.3)
3	0.8 (0.6 to 0.9)
4	0.7 (0.5 to 0.9)
6	0.8 (0.6 to 1.1)

* participants versus non-participants, i.e., non-responders + refusers
† OR = Odds Ratio; CI = Confidence Interval; from a logistic regression model
‡ reference category
¶ due to exclusion of 4 clinics (see *Methods* section) clinic numbers are not sequential

Finally, we assessed variation in participation rates by population characteristics in a multivariate model (Table 3.6). In general, the multivariate analysis confirmed the results of the earlier-described crude analysis (Table 3.4). However, after adjustment for the other factors of interest, subjects who had been included in the 1985 survey, were more likely to participate in the current survey compared to subjects who were contacted for the first time, which was not seen in the crude analysis. The differences in participation rate by age and treatment and clinic remained apparent after adjustment for other relevant characteristics. Similar models were repeated for both non-responders (compared to participants + refusers) and refusers (compared to non-responders + participants). The results were comparable to the patterns described in Table 3.5, i.e., a trend of increasing refusal rates with increasing age and a tendency for male non-participants to not respond, as opposed to refuse. For exposure status no strong separate effect of either non-response or refusal was observed (not shown).

Discussion

The decline of participation rates has become a major focus of observational studies [17]. As evidence from different studies in various types of populations remains conflicting [3,4,6,7], we conducted a randomized study to examine the effect of questionnaire length on participation rate in a sample of a population treated for ear, nose and throat conditions in childhood. A substantial difference in participation rate according to questionnaire length was noted. Although not statistically significant, the difference was judged large enough to use a shortened questionnaire in the final questionnaire survey.

The use of a multi-option type of informed consent form versus a basic form did not affect participation rates. The choice of a consent form for the final survey therefore had to be based on other grounds. The multi-option consent form was conceived to offer the possibility of partial consent to cohort members with strong views regarding the privacy surrounding their medical history and future medical conditions. Nevertheless, only 8 percent of the participants of the subgroup to whom we offered the possibility of partial consent actually used this option. Among the six subjects who gave partial consent, three had misunderstood the form and their data could not be used for the study. Taking into account the small proportion of subjects who used the possibility of partial consent and the practical problems imposed by different combinations of partial consent, we decided to use a basic type of consent form in the final survey.

Despite the small sample, the results of the randomized study provide insight into the effects of questionnaire length and type of consent form in a population exposed to medical treatments in (early) childhood, after a follow-up of several decades. We are not aware of other reports on the effects of the use of different consent forms in mailed questionnaire surveys.

The NRI questionnaire survey resulted in a final participation rate of 74 percent, which is 10 to 15 percent lower compared to the previous follow-up of part of this cohort [8] and in a similar US-based survey conducted in 1980 among 3000 subjects treated at an ENT clinic in childhood [18]. Yeh at al [19] recently reported on prolonged follow-up of the US cohort, with a participation rate of 90 percent among subjects who had responded to the 1978 questionnaire. Participation rates well above 80 percent were also reported in written health questionnaire surveys among other US cohorts of subjects irradiated in childhood or young adulthood [20,21] conducted before 1990. All three studies [19-21] were based on single hospital cohorts, and the follow-up studies were conducted by the same centers, whereas our study was multi-center, with an external coordinating center. This might have contributed to the lower participation rate in our study. Nevertheless, even when we limited the analysis to participants in the 1985 survey known to be alive in 1997, the participation rate was still lower (77 percent) compared to the US cohorts.

A general decline in the willingness to participate in epidemiologic surveys has recently been noted and is thought to be due, at least in part, to the increased frequency of commercial surveys [17]. It might also be related to increased (media) attention paid to potential privacy problems related to medical record research, and to the introduction of new privacy-associated laws and subsequent public awareness of these issues [22-24]. Unfortunately, we were unable to check this assumption as only a small proportion of subjects who chose not to participate commented on the reason for not participating, whereas no such data are available for the true non-responders in our study.

Analysis of the separate contribution of successive approach strategies revealed that both the reminder mailing and the telephone survey contributed substantially to final participation rates, particularly in the younger age groups. The telephone survey also appeared to be particularly useful for explaining study procedures, and providing information on the NRI treatment for subjects who did not recall, or had never been informed by their parents, what NRI was all about. Additional home visits did not contribute further, as was also reported in a meta analysis of German case-control studies [25].

In agreement with several other studies on the late health effects of childhood radiation exposures [18,21,26] we found a statistically significantly lower participation rate among non-exposed subjects. Initially, we suspected that this observation might be related to age at treatment, i.e., that subjects who did not participate were those who where unaware of

treatment by an ENT-physician in the past because they were so young at that time (<5 years). Indeed, adjusted for attained age, there was an effect of age at treatment in that those treated in infancy were less likely to participate, but this tendency was seen in both exposed and non-exposed subjects.

Higher participation rates among females and younger subjects have been reported in some, but not all studies [3,6,7,13]. This may depend on the age-distribution in the cohort, the topic of the research, and the number of attempts to contact non-responders.

In interpreting these results, methodological aspects of the study deserve attention. The follow-up was conducted through municipal registries, thus ensuring a very high probability of contacting the cohort member at the correct address. Population characteristics were taken from individual medical charts and double-checked during the follow-up, thereby reducing misclassification.

In summary, we reported on characteristics of participation in a retrospective cohort study of subjects mostly treated at childhood ages. Questionnaire length appeared to be an important determinant of the participation rate, whereas the option to choose for partial consent, in comparison to overall consent, did not influence the participation rate, but was confining to a small proportion of participants. A reminder mailing and a telephone survey added substantially to the final participation rate, whereas additional home visits did not. Attained age, sex, exposure status, age at treatment, and having participated in a former follow-up were important determinants of participation rates.

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4

Long-term cancer incidence following nasopharyngeal radium irradiation

Summary

From 1940 through 1970, nasopharyngeal radium irradiation (NRI) was used widely to treat children and military personnel suffering from Eustachian tube failure due to local lymphoid hyperplasia. We studied cancer incidence in a cohort of 4,339 Dutch patients, treated with NRI mostly in childhood, and 4,104 frequency-matched non-exposed subjects. Average doses to the nasopharynx, pituitary gland, brain and thyroid gland were 275, 11, 1.8 and 1.5 cGy, respectively. Cancer incidence was assessed from cancer registry linkage (1989-1996), self-report including medical verification (1945-1988) and death certificates (1945-1996). During a 18-50 year follow-up, fourteen malignancies of the head and neck occurred among exposed subjects (SIR 1.2, 95% CI: 0.6-2.8). These included four thyroid malignancies (SIR 2.8, 95% CI: 0.8-7.2) and five malignant brain tumors (SIR 1.3, 95% CI: 0.4, 3.1). Increased risks were observed for malignancies of lymphoproliferative and hematopoietic origin (SIR 1.9, 95% CI: 1.2, 2.8) and breast cancer (SIR 1.5, 95% CI: 1.1-2.1). In the non-exposed group, SIRs for most cancer sites were close to unity. Strong dose-response trends could not be demonstrated for any cancer outcome although relative risks were elevated in the highest dose category for head-and-neck cancer and breast cancer. These data provide little evidence for a high excess risk of cancer associated with NRI treatment. Inconsistent findings across studies and public concern warrant further prolonged follow-up of available cohorts.

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Introduction

Recent results of follow-up studies in radiation-exposed populations showed elevated risks for malignancies of the brain, thyroid and salivary glands among childhood cohorts treated for tinea capitis, haemangioma and enlargement of thymus, adenoid or tonsils in the decades before 1960 [1-5]. The treatments for these benign head and neck conditions typically involved external beam radiation (X-rays) with low to moderate radiation exposures to the head and neck (e.g., thyroid gland 0.1-1.4 gray (Gy); brain > 1 Gy).

During the same time, nasopharyngeal radium irradiation (NRI) was used widely to ameliorate Eustachian tube dysfunction and decrease hearing loss in children suffering from chronic otitis serosa or recurrent adenoid growth [6]. NRI was also used in WW-II military personnel with aerotitis media [7]. This treatment consisted of insertion of a radium capsule through the nostrils to shrink accumulated lymphoid tissue in the nasopharynx. NRI treatments typically involved comparatively low radiation doses to the head and neck (e.g., thyroid gland <.05 Gy; brain < 0.2 Gy) [8]. At least 8,000 servicemen and 0.5 to 2.5 million children are thought to have been treated with NRI in the U.S. [9,10].

Prompted in part by public concern raised in the early 1990s [11-13], cohort studies were undertaken to address the late health effects of NRI. Statistically non-significant excesses were reported for head and neck cancer fatalities among 1,214 NRI-treated WW-II submariners [14] and for brain tumors among 904 U.S. children [15,16]. In The Netherlands, more than 24,000 children were treated with NRI [17]. We studied a cohort of over 4,000 of these patients [18,19], and observed no excess of head and neck cancer mortality in this group [18]. Here we report on cancer incidence in this cohort, allowing for the evaluation of a greater number of cancer cases and for the study of cancers with a generally good prognosis, such as thyroid cancer.

Methods

Study population

Building on a previously defined cohort [19] we recruited an expanded cohort of patients who had been treated by ear-nose-and-throat (ENT) physicians between 1945 and 1981, in the ENT departments of nine clinics in The Netherlands. We identified 5,358 eligible patients ever treated with NRI and a frequency-matched (by clinic, sex, birth & first treatment year) non-exposed

group of 5,265 subjects who had also been treated for ENT conditions, but had never been exposed to NRI. Institutional review boards of all participating hospitals and research institutes approved the study protocol. Detailed descriptions of data collection, follow-up and dosimetric methods have been reported elsewhere [18,19].

Medical record data

Exposure status was determined from the individual ENT treatment charts. Diagnosis at first consultation was coded and, for exposed subjects, individual treatment characteristics including date and duration of each treatment session were recorded on a data-collection form.

Radiation dosimetry

NRI-treatment protocols varied by clinic. In most clinics, one treatment course typically consisted of three or four 7-15 minute sessions, separated by intervals of one or two weeks. The treatments ranged from 3 to 74 milligram-hours (mgh: mg radium multiplied by treatment duration in hours). Organ-specific doses were calculated based on simulations in age-appropriate, anthropomorphic phantoms, taking into account the distance from the radium applicator to the organ of interest [8,18]. Mean tissue doses to nasopharynx, pituitary gland, brain and thyroid gland were 275, 10.9, 1.8 and 1.5 cGy, respectively, whereas mean tissue absorbed doses to the total active bone marrow (ABM) and breast were only 0.4 and 0.1 cGy, respectively [18]. We also calculated average dose for head and neck ABM (average 1.9, range 0.3-8.1 cGy). To evaluate dose-related risk of non-Hodgkin's lymphoma (NHL) we defined five regions of lymphoproliferative tissues throughout the body. Qualitatively defined doses for these regions ranged from very high (nasopharynx and tonsillar region) to virtually zero (below diaphragm).

Follow-up

Cohort members were traced through September 15, 1997 at municipal resident registries to determine vital status and address (if living). For untraceable subjects, additional searches were carried out at the Dutch Ministry of Foreign Affairs, and at the Central Bureau of Genealogy, a

nationwide registry of deceased Dutch citizens. In all, 92 percent of both exposed and non-exposed subjects were successfully traced.

Assessment of cancer incidence

Cancer incidence was assessed through record linkage with The Netherlands Cancer Registry (NCR) for the period 1989-1996 and through a health questionnaire survey coupled with medical verification of self-reported tumors for the period 1945-1988 (see below). For decedents, cause of death information was obtained from Statistics Netherlands, coded according to revisions of the ICD applicable in the calendar period of death. For this study all registered causes from earlier revisions were re-coded according to the 9th revision [20]. If a subject died of cancer, but did not have a cancer diagnosis in the period 1989-1996, the cause and date of death were used as proxies for cancer incidence data.

Health questionnaire survey

A questionnaire, a letter of introduction from an ENT-physician of the hospital where the subject was treated, and an informed consent form were mailed to each living subject in the cohort, as of 1997. Exposed and non-exposed subjects received identical letters. Consent was obtained for release of personal and medical data from participating ENT physicians, maintenance of the study-database including personal identifiers for prospective follow-up, and record linkage with The Netherlands Cancer Registry.

We defined three response-groups: (a) subjects who completed and returned the questionnaire and the consent form (participants), (b) others who responded that they did not want to participate (refusers) and (c) non-responders. Refusers were not contacted again. Four weeks after the first mailing, all non-responders received a reminder letter with a questionnaire and a consent form. Both the original and the reminder letter stated explicitly that the consent form should be returned blank if the subject chose not to participate in the study. Eight weeks after the first mailing, registered telephone numbers of all non-responders were traced through a linkage with the computer database of the Public Telephone Company and by additional manual searches. If the number was traced, the non-responder was contacted and asked to complete the questionnaire with the interviewer, over the phone. Eventually, of all cohort members alive as of 1997, 71.4 percent participated, 14.2 percent refused and 14.4 percent were non-responders.

The questionnaire contained 43 items covering socio-demographic items, diseases that are known or suspected to be related to radiation exposure in the head-and-neck area, (cancer, thyroid disease, reproductive failure) and possible confounders (occupation, smoking, alcohol consumption, exposure to various radiation sources and female reproductive characteristics). We identified participants who had potentially been diagnosed with a malignancy by including items on cancer, tumors and "growths". Other indicative items concerned hospital admissions, biopsies and radiation treatments. In case of an affirmative answer to one or more of the latter items, we sent a new letter asking for the name of the treating physician and for completion of a second consent form to allow release of medical data for study purposes. If consent was obtained, the physician was asked for a pathology report of the self-reported disorder, and copies of relevant correspondence or medical chart notes.

In addition to the medically confirmed cancer cases we included three self-reported but medically unconfirmed cases, in which the questionnaires contained unequivocal information on organ site and malignant nature of the disease. By the time we re-contacted these participants to seek written consent for medical confirmation, they were either too ill (breast and ovarian cancer) or had died (lung cancer), as reported to us by the respective family members.

Linkage with The Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) provided data for the period 1989 to 1996 only, as the nationwide registry was not yet fully operational before 1989. Completeness has been estimated to be 96 percent [21,22]. The linkage is based on a unique code consisting of the first four digits of the last name, sex, and birth date [23]. Linkage results were coded according to both the International Classification of Oncology (ICD-O) [24] and the ICD-9 [20]. Furthermore, date of diagnosis, source of diagnosis and tumor-stage were provided. Linkage was allowed for all living and deceased subjects, except for those who explicitly refused participation.

Definition of analytic cohort

From the total cohort of 10,623 subjects, 340 (3%) were excluded due to loss of follow-up, 524 (5%) due to emigration, and 1,314 (12%) because they refused to participate in the survey. Further, two decedents were excluded because the cause of death could not be obtained from

Table 4.1
Distribution of subjects, person-years of observation and cancer cases by exposure status

	NRI-Exposed group		Non-exposed group	
	N	PY	N	PY
Eligible study cohort				
Alive, Responder	3,440	108,014	3,088	102,122
Alive, Non-responder	598	18,037	702	22,205
Deceased	301	7,188	314	7,780
Overall	4,339	133,239	4,104	132,105
Cancer case status				
Alive	65		56	
Deceased	103		98	
Excluded from present analyses				
Emigrants	265		259	
Lost to follow-up	167		173	
Alive, Refusal	586		728	

Statistics Netherlands. The cohort for the present analyses comprised 4,339 exposed and 4,104 non-exposed subjects (Table 4.1). All cancers, including multiple primaries, are included in the analyses, except for non-melanoma skin cancers.

Calculation of person-years

Person-years were accumulated from the date of first treatment until the date of first tumor diagnosis, date of death or September 15, 1997, whichever came first. Among non-responders, person-years were accumulated through December 31, 1996, i.e., the last date covered by the NCR-linkage. In a supplementary analysis, which included NCR-determined cases only, person-year calculation was restricted to the time-window from January 1, 1989 through December 31, 1996.

Statistical analysis

First, we compared observed numbers of cancers (O) in the exposed and unexposed groups with expected numbers (E) based upon Netherlands population statistics. Expected numbers were calculated by applying the person-year distribution in the cohort to sex-, age- and calendar period-specific reference data from the NCR [25,26]. As nationwide data were only available for the years from 1989 onwards, we used reference data from the oldest Dutch regional Cancer

Registry (Comprehensive Cancer Center South, Eindhoven) for the period between 1973 and 1988 [27,28], with extrapolation of the 1973-1975 rates to all earlier years (1940-1972).

Data were aggregated by calendar period of follow-up (1940-1949, 1950-1959, ..., 1990-1997), sex, attained age (0-4, 5-9, 10-19, ... ,70-79 and ≥80 years), treatment prescription dose (non-exposed, <10, 10-19, 20-29, 30-39 and ≥40 mgh), age at treatment (0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, and ≥50 years) and clinic. For each cell the number of person-years and numbers of observed and expected cases of specific cancers were calculated, as well as person-year weighted averages of attained age, age at treatment and organ-specific radiation doses. Standardized Incidence Ratios (SIR), defined as the O/E ratio, were then obtained and 95% Confidence Intervals (CI) were calculated using Poisson assumptions for the observed frequencies [29,30].

Second, we directly compared the relative risks (RR) of cancer between NRI-exposed and unexposed groups by Poisson regression using the cell-specific expected frequencies as surrogates for person years [31]. That is, for each cell, the observed frequency was assumed to correspond to a Poisson variable with a mean equal to the expected frequency of the population (E), treated as known, times a parametric function that depended on exposure or estimated radiation dose (D). Thus, the model for comparing non-exposed subjects and NRI-exposed subjects was mean (O) = αE for non-exposed subjects and $\alpha E(1+\beta)$ for NRI-exposed subjects, where α and β are unknown parameters, RR = $1+\beta$, and the excess RR (ERR) = β. For comparison specific to radiation dose, the linear model is mean (O) = $\alpha E(1+\gamma D)$, where γD = the ERR at dose D and the unknown parameter γ = ERR per unit dose.

We also conducted analyses that included a variable indicating year of diagnosis before or after 1989 to adjust for the elevated potential for case finding after 1989. As none of the RR-estimates was substantially altered, these analyses are not presented.

Finally, we divided the body in five anatomically defined dose regions (see dosimetry), as surrogates for dose at lymphoid tissues, in order to evaluate risk of NHL by dose region. For comparison, we obtained NHL reference rates by anatomic site from the Maastricht Cancer Registry (1986-1998) from which we derived dose-region specific expected numbers of NHL. For each dose-region, the expected numbers of NHL cases was then compared to the actual observed number of NHL cases.

Results

NRI-exposed and non-exposed subjects were similar with regard to gender, age, and follow-up time characteristics (Table 4.2). The majority of exposed subjects had their first radiation treatment before age ten, were followed for 20-40 years, and were between 30 and 59 years old at the end of follow-up (Table 4.2). The proportion of subjects treated before age five was greater among non-exposed compared to exposed subjects, because we matched the non-exposed group on age at first consultation rather than age at first radiation treatment.

In the exposed group (Table 4.3), a total of 168 cancer cases were observed compared to 142 expected (SIR 1.2). We observed fourteen malignancies in the head and neck area (SIR = 1.3), including four thyroid malignancies (two papillary and two follicular tumors) (SIR = 2.8; 95% CI: 0.8 to 7.2), two pharyngeal cancers (SIR = 2.0, 95% CI: 0.0 to 7.2) and five brain cancers (ICD9: 191) (SIR = 1.3, 95% CI: 0.4 to 3.1). Three of the brain cancers were astrocytoma and two were malignant, but of unknown histology. Not included in the present analyses were two fatal brain neoplasms of unspecified nature (ICD-9: 239.6) [18].

Table 4.2
Population characteristics of The Netherlands NRI cohort by exposure status

	Exposed No. (%)†	Non-exposed No. (%)
Gender		
Male	2,471 (57)	2,324 (57)
Female	1,868 (43)	1,780 (43)
Age at first treatment (years)*		
0-4	917 (21)	1,732 (42)
5-9	2,255 (52)	1,254 (31)
10-14	547 (13)	444 (11)
15-19	144 (3)	208 (5)
≥20	476 (11)	466 (11)
Follow-up (years)		
<20	427 (10)	388 (10)
20-29	1,476 (34)	1,363 (33)
30-39	1,581 (36)	1,458 (36)
≥40	855 (20)	895 (22)
Attained age (years)		
<30	633 (15)	667 (16)
30-39	1,275 (29)	1,255 (31)
40-49	1,382 (32)	1,178 (29)
50-59	631 (15)	579 (14)
≥60	418 (10)	425 (10)

* Date of first treatment refers to first radium treatment session among exposed and to first consultation among control subjects
† Due to rounding percentages do not always add up to 100%

Table 4.3
Cancer incidence in The Netherlands NRI study, by exposure status

Tumor site*	NRI-Exposed group		Non-exposed group		Direct comparison
	O	SIR (95% CI)	O	SIR (95% CI)	RR (95% CI)†
Head and neck area‡	14	1.3 (0.7, 2.2)	11	1.1 (0.6, 2.0)	1.2 (0.6, 2.8)
Brain	5	1.3 (0.4, 3.1)	6	1.7 (0.6, 3.7)	0.8 (0.2, 2.9)
Thyroid	4	2.8 (0.8, 7.2)	1	0.7 (0.02,4.1)	3.8 (0.5, 76.0)
Pharynx	2	2.0 (0.02, 7.2)	0	(0.0, 4.0)	
Oral cavity	1	0.5 (0.01, 2.9)	2	1.1 (0.01, 4.1)	0.7 (0.03, 7.2)
Larynx	2	1.1 (0.01, 4.0)	2	1.2 (0.01, 4.3)	0.7 (0.09, 6.3)
Lung	28	1.4 (0.9, 2.0)	26	1.4 (0.9, 2.0)	1.0 (0.6, 1.8)
Digestive tract	32	1.2 (0.9, 1.8)	34	1.4 (0.9, 1.9)	0.9 (0.6, 1.5)
Breast	36	1.5 (1.1, 2.1)	24	1.0 (0.6, 1.5)	1.6 (0.9, 2.7)
Female genital tract	6	0.5 (0.2, 1.2)	12	1.0 (0.5, 1.8)	0.5 (0.2, 1.3)
Cervix	1	0.2 (0.00, 1.0)	6	1.1 (0.4, 2.4)	0.2 (0.02, 1.2)
Ovary	3	1.0 (0.2, 2.8)	5	1.5 (0.5, 3.5)	0.6 (0.1, 2.3)
Uterus	1	0.5 (0.01, 2.7)	1	0.4 (0.01, 2.3)	0.8 (0.03,21.3)
Prostate	3	0.5 (0.1, 1.4)	6	1.1 (0.4, 2.4)	0.5 (0.09,1.8)
Hematopoietic and Lymphoproliferative¶	25	1.9 (1.2, 2.8)	12	0.9 (0.5, 1.6)	2.3 (1.1, 4.8)
NHL	12	2.3 (1.2, 4.1)	5	1.0 (0.3, 2.4)	2.7 (1.0, 8.7)
Hodgkin's Disease	1	0.3 (0.01, 1.9)	2	0.7 (0.01,2.5)	0.9 (0.04,24.3)
Multiple Myeloma	4	3.1 (0.9, 8.0)	0	(,3.0)	
Leukemia#	8	2.0 (0.9, 4.0)	5	1.3 (0.4, 2.9)	1.9 (0.6, 6.5)
Unspecified	6	1.7 (0.6, 3.8)	5	1.5 (0.5, 3.5)	1.1 (0.6, 6.5)
All sites combined §	168	1.2 (1.0, 1.4)	154	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)

O = observed number of cases, E = expected number of cases, SIR = standardized incidence ratio (O/E), RR = relative risk, CI = confidence interval
* multiple primaries included in analyses: among exposed (N=8): one case each of cancer of the stomach, rectum, anus, pancreas, breast, eye, multiple myeloma and chronic myeloid leukemia (third primary); among non-exposed (N=5): one cancer each of the breast, colon, cervix, uterus, and acute myeloid leukemia
† relative risk obtained from Poisson Regression, adjusted for attained age and age at treatment
‡ defined as International Classification of Diseases - 9th edition [20] codes 140-149, 160,161,191,193;
¶ defined as International Classification of Diseases - 9th edition [20] codes 200-208;
\# subtypes of leukemia (number of cases), among exposed: acute lymphoblastic (one), chronic lymphoblastic (one), acute myelocytic (one), chronic myelocytic (three), subacute myelocytic (one) and unspecified (one); among non-exposed: acute lymphoblastic (one), acute myelocytic (two), acute monocyte (one) and acute erythrocyte (one).
§ numbers do not add up tot total as not all tumor sites are mentioned in table

Table 4.4
Cancer incidence in The Netherlands NRI study, defined by cancer registry linkage (1989-1996)

Tumor site*	NRI-exposed group		Non-exposed group		Direct comparison
	O	SIR (95% C.I.)	O	SIR (95% C.I.)	RR (95% C.I.)‡
Head and neck area	4	0.8 (0.2, 2.0)	3	0.6 (0.1, 1.9)	1.2 (0.3, 6.3)
Breast	23	1.8 (1.2, 2.7)	8	0.7 (0.3, 1.3)	2.8 (1.3, 6.6)
Hematopoietic and Lymphoproliferative	10	1.8 (0.8, 3.2)	4	0.7 (0.2, 1.9)	2.4 (0.8, 8.6)
NHL	7	2.7 (1.1, 5.6)	3	1.3 (0.3, 3.7)	2.2 (0.6, 10.1)
All sites combined†	72	1.0 (0.8, 1.3)	71	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)

O = observed number of cases, E = expected number of cases, SIR = standardized incidence ratio (O/E), RR = relative risk, CI = confidence interval, NHL = non-Hodgkin's lymphoma
* presented observed numbers include three second tumors among exposed i.e., colon after rectal cancer, rectal after prostate cancer, and multiple myeloma after prostate cancer.
† numbers do not add up as not all tumor sites are mentioned in Table
‡ relative Risk obtained from Poisson Regression, adjusted for attained age and age at treatment

Risk of malignancies of hematopoietic and lymphoproliferative origin was elevated among exposed subjects (SIR = 1.9, 95% CI: 1.2 to 2.8), mainly due to excesses risk of NHL (SIR = 2.3, 95% CI: 1.2 to 4.1). Statistically nonsignificant, elevated risks were also observed for multiple myeloma (SIR=3.1) and leukemia (SIR = 2.0). We also observed elevated risk of breast cancer in the exposed group based on 36 cases (SIR = 1.5, 95% CI: 1.1 to 2.1), whereas the overall risk of female genital tract cancers was nonsignificantly decreased, mainly due to a deficit of cervical cancer. For other major cancer sites, no excesses were found (Table 4.3).

In the non-exposed group, none of the SIRs was statistically significantly different from unity. The direct comparison of the exposed to the non-exposed group in terms of RRs was similar to the pattern for the SIRs in the exposed group, although with much wider CIs (Table 4.3). Results for cancer sites of interest were similar when the analysis was restricted to cancers ascertained by NCR only (and, therefore, limited to the time period 1989-1996) (Table 4.4).

We then assessed variability in risk among exposed subjects by age at treatment (Table 4.5) and time since treatment (Table 4.6). For malignancies of hematopoietic and lymphoproliferative origin, more cases were observed than expected among subjects treated at 10 years of age or older (SIRs 3.7 and 2.0 for categories 10-19 and ≥20 years, respectively), whereas for breast cancer, SIRs were (non-significantly) elevated among women treated at 5 to 19 years of age (SIRs 1.8 and 1.7 for categories 5-9 and 10-19 yrs, respectively) (Table 4.5). Except for breast cancer, about half of all cancer cases were observed in subjects treated with NRI at adult ages. Among non-exposed subjects, no clear patterns of risk were seen with age at treatment (not shown).

The analysis by time since initial treatment revealed slightly elevated SIRs for total cancer more than 20 years after treatment (Table 4.6). For head and neck cancers the SIR was

Table 4.5
Cancer incidence for selected tumor sites among exposed subjects, by age at treatment

Age at treatment (yrs)‡	O	SIR*	(95% CI)	p† (trend)
		All cancers		
<5	12	1.2	(0.6 - 2.1)	
5-9	37	1.0	(0.7 - 1.4)	
10-19	27	1.1	(0.7 - 1.6)	
≥20	92	1.3	(1.0 - 1.6)	0.24
		Head and neck area		
<5	2	1.9	(0.0 - 6.9)	
5-9	3	0.9	(0.2 - 2.5)	
10-19	2	1.0	(0.0 - 5.3)	
≥20	7	1.7	(0.7 - 3.5)	0.44
		Lymphoproliferative and hematopoietic		
<5	2	1.1	(0.0 - 4.1)	
5-9	6	1.2	(0.5 - 2.7)	
10-19	8	3.7	(1.6 - 7.2)	
≥20	9	2.0	(0.9 - 3.8)	0.48
		Female breast		
<5	2	1.1	(0.0 - 4.1)	
5-9	15	1.8	(1.0 - 3.0)	
10-19	11	1.7	(0.9 - 3.1)	
≥20	8	1.1	(0.5 - 2.2)	0.32

* standardized incidence ratio
† Chi-square test for trend for SMRs described by Breslow and Day [30]
‡ Number of person-years per category: 28,282 – 70,302 – 22,175 – 12,480, respectively

significantly elevated in the third decade after treatment (SIR = 2.8, 95% CI: 1.2 to 5.5) (when all four thyroid cancers were observed), but not thereafter. Although SIRs for malignancies of lymphoproliferative and hematopoietic origin tended to be elevated in all follow-up intervals, the highest risk estimate was observed 20-29 years after treatment (SIR = 3.1, 95% CI: 1.6 - 5.6). Risk of breast cancer showed a statistically significant trend with time since treatment ($p<.05$), with the highest risk among women treated with radium more than 30 years earlier (SIR = 2.0, 95% CI: 1.3 to 3.0). In the non-exposed group, the SIR for total cancer was elevated after more than 30 years of follow-up (SIR 1.4, 95% CI: 1.1 to 1.7) (not shown). Table 4.7 shows RRs by categories of appropriate tissue dose for malignancies of interest. Compared to the non-exposed group, RRs for cancers in the head and neck area rose with increasing dose up to 3.1 among those exposed to more than 600 cGy in the nasopharynx (p-trend = 0.06). Modeled as a continuous dose, the ERR/cGy was 0.002 (95% CI: -0.00006 to 0.008). Dose-related risk estimates for brain cancer (ERR/cGy = 0.04 [95% CI: -0.03 to 0.3]; p-trend=0.39) and thyroid

Table 4.6
Cancer incidence for selected tumor sites among exposed subjects, by time since treatment

Time since treatment (yrs)‡	O	SIR*	(95% CI)	p† (trend)
		All cancers		
<10	16	0.9	(0.5 - 1.5)	
10-19	29	0.9	(0.6 - 1.3)	
20-29	54	1.4	(1.0 - 1.8)	
≥30	69	1.3	(1.0 - 1.6)	0.10
		Head and neck area		
<10	3	2.2	(0.5 - 6.4)	
10-19	1	0.4	(0.0 - 2.3)	
20-29	8	2.8	(1.2 - 5.5)	
≥30	2	0.5	(0.0 - 1.9)	0.41
		Lymphoproliferative and hematopoietic		
<10	3	1.3	(0.3 - 3.7)	
10-19	5	1.4	(0.5 - 3.3)	
20-29	11	3.1	(1.6 - 5.6)	
≥30	6	1.5	(0.6 - 3.3)	0.55
		Female breast		
<10	1	0.5	(0.0 - 2.7)	
10-19	3	0.9	(0.2 - 2.5)	
20-29	8	1.3	(0.6 - 2.5)	
≥30	24	2.0	(1.3 - 2.0)	0.03

* standardized incidence ratio
† Chi-square test for trend for SMRs described by Breslow and Day [30]
‡ Number of person-years per category: 43,162 - 41,359 – 30,555 – 18,161, respectively

cancer (ERR/cGy=1.51, 95% CI [undetermined negative lower bound to 46], p-trend=0.25), were unstable due to small numbers.

RRs for NHL were highest in the low (RR=4.4) and the high (RR=3.4) total ABM dose groups with no evidence of a dose-response trend (p=0.14); Similarly, RRs by dose to the head and neck ABM were 3.0 for low dose, 1.5 for medium dose, and 3.7 for high dose (data not shown). For leukemia, no dose-response was observed for total ABM (p-trend=0.47, Tabel 4.7) or for dose related to head and neck ABM (data not shown). All multiple myeloma cases received an ABM radiation dose in the medium (N=1) or high dose (N=3) categories; the corresponding ERR/cGy of total ABM dose was 199, with an extremely wide confidence interval (p-trend =0.0006) . As NRI was used to treat lymphoid tissue hyperplasia, we also evaluated NHL risk by local lymphoid tissue dose. The NHL cases with known location (11 of 12) were grouped by primary site of first presentation and compared to expected numbers per anatomically defined dose region. Known sites in the head and neck area included the parotid gland (N=1), base of tongue (N=1) and the cervical lymph nodes (N=2). SIRs tended to be elevated for all dose

categories, but, confidence intervals were wide and overlapping. The SIR for NHL in the head and neck area combined was 2.3 (95% CI: 0.6 to 5.9).

Risk for breast cancer was statistically significantly elevated (RR=2.6) among females in the highest dose category (>0.2 cGy) (Table 4.7). The ERR/cGy was a marginally significant 4.8 (95% CI: 0.2 to 13.3). For the subset of women who provided questionnaire information on breast cancer risk factors (Table 4.8), adjustment for the number of children, age at first birth (among parous women) or age at menarche did not alter the risk estimates (data not shown).

When restricted to exposed subjects only, category-specific RRs for head and neck cancers tended to increase monotonically with dose, whereas for breast cancer, elevated risk was restricted to the high-dose group. There was no evidence of a monotonic trend of increasing RRs with increasing total ABM dose for leukemia and NHL (Table 4.7).

Table 4.7
Evaluation of radiation dose effects for selected cancer sites in The Netherlands NRI cohort study

Dose category	mean dose (cGy)	E	O	RR*	(95% CI)	p† (trend)
			Head and neck area			
Non-exposed	0	10.0	11	1.0‡		
Low[a]	139	3.7	2	0.5	(0.1 - 1.9)	
Medium	299	4.6	6	1.1	(0.4 - 3.1)	
High	613	2.4	6	3.1	(1.0 - 8.6)	0.06
			non-Hodgkin's lymphoma			
Non-exposed	0	4.9	5	1.0‡		
Low[b]	0.18	2.2	6	4.4	(1.2-17.2)	
Medium	0.35	1.9	3	1.5	(0.3 - 6.4)	
High	0.77	1.1	3	3.4	(0.7-14.9)	0.14
			Leukemia			
Non-exposed	0	4.0	5	1.0‡		
Low[b]	0.18	1.7	4	2.5	(0.6-11.1)	
Medium	0.35	1.5	3	1.6	(0.3 - 7.1)	
High	0.77	0.7	1	1.4	(0.1 - 8.9)	0.47
			Female breast			
Non-exposed	0	24.2	24	1.0‡		
Low[c]	0.01	6.2	7	1.2	(0.4 - 2.6)	
Medium	0.11	13.3	19	1.5	(0.8 - 2.8)	
High	0.29	4.3	10	2.6	(1.1 - 5.7)	0.03

E = expected number of cancers, O = observed number of cancers , RR = relative risk, CI = confidence interval
* relative risk and confidence intervals obtained from Poisson Regression model, adjusted for attained age and age at treatment
† test for trend = Likelihood Ratio test for adding continuous dose variable to null model
‡ reference category
# woman-years
¶ RRs not shown in view of small number of cases and unstable estimates
a = nasopharyngeal dose; b = total active bone marrow (ABM) dose; c = breast dose

Table 4.8
Distribution of potential confounders among questionnaire survey participants of The Netherlands NRI cohort study by exposure status

Factor *	NRI-exposed group No.	%	Non-exposed group No.	%	p (χ2 test)
Age at menarche‡					
<12 yrs	217	14	206	15	0.61
12-14 yrs	1,100	70	958	68	
>14 yrs	235	15	229	16	
Unknown	27	1	21	1	
No. of children‡					
None	486	31	485	34	0.09
1-2	825	52	714	51	
3-4	246	16	188	13	
>4	15	1	17	1	
Unknown	7	<1	10	<1	
Age at first birth‡§					
<25 yrs	373	34	320	34	0.26
25-29 yrs	476	44	383	41	
30-34 yrs	198	18	164	18	
>34 yrs	28	3	37	4	
Unknown	18	2	25	3	
Menopausal status‡					
pre-menopausal	1,018	64	910	64	0.83
post-menopausal	308	20	286	20	
Unknown	253	16	218	15	
No. chest X-rays (age <20) ¶					
0	1,834	53	1,650	53	0.95
1-5	586	17	515	17	
6-10	77	2	64	2	
>10	37	1	38	1	
Unknown	906	27	821	27	
Highest level of education					
Low	844	25	754	24	0.11
Medium	1,460	42	1,343	44	
High	1,064	31	902	29	
Unknown	72	2	89	3	
Smoking status					
Never	1,368	40	1,209	39	<0.05
<10 packyears	829	24	797	26	
10-29 packyears	851	25	696	23	
30+ packyears	253	7	229	7	
Unknown	139	4	157	5	
Alcohol consumption†					
none	696	20	653	21	<0.01
<1 glass/day	1,168	34	1,124	37	
1-2 glasses/day	1,081	31	819	27	
3-5 glasses/day	306	9	291	9	
>5 glasses/day	56	2	61	2	
Unknown	133	4	140	4	

* total number of participants 3,440 among exposed and 3,088 among non-exposed;
† refers to alcohol consumption during year preceding the 1997-questionnaire survey ;
‡ among females only; total number of female participants: 1,579 exposed and 1,414 non-exposed
§ percentage related to total number of parous women.
¶ sum of chest X-rays ("lung views") and tuberculosis screening X-rays

Discussion

Our study of cancer risk in a cohort of Dutch patients treated with NRI in the post-WW-II decades does not indicate highly elevated risks of cancer in general, or of tumors in the head and neck area in specific. The three-fold, statistically non-significant, increased risk of thyroid cancer is however intriguing. We observed a 1.9-fold increased risk of malignancies of lymphoproliferative and hematopoietic origin and a 1.5-fold increased risk of breast cancer. Except for thyroid cancer, these results reflect the pattern of cancer mortality in this cohort [18].

So far, there has been no indication of pharyngeal tumor induction in any of the NRI cohorts [15,33], although pharyngeal tissues received the highest radiation dose during treatment [8]. We observed only two pharyngeal cancers, against one expected. As pointed out by Royal [34], much of the pharyngeal tissue is exposed to radiation doses in the cell-killing range, which might mask any carcinogenic effect.

We did observe a three-fold, but statistically non-significant, increased risk of thyroid cancer. Such a high RR has not previously been associated with an average thyroid dose as low as 1.5 cGy, although a recent pooled analysis of seven cohorts showed a significant dose-response association down to 10cGy [3]. In a Maryland NRI cohort, two thyroid cancers were seen among 914 NRI-exposed subject (RR=4.2, 95% CI: 0.4 to 46.6) with a median thyroid radiation dose of 9 cGy [15]. Although the small numbers prevent any definitive conclusions, the results are intriguing.

We found no more brain cancers than expected, compared to a 14.8-fold, but statistically non-significant, elevated risk in the Maryland NRI cohort, based on 3 cases [15]. The dose to the brain in the Maryland cohort was estimated to be 15-40 cGy (Shore, 1982 [35], cited in Land, 1986 [36]), i.e, substantially higher than the average brain dose in our cohort (1.8 cGy, range, 0.3 - 8 cGy) [18]. Hazen et al [33] observed no elevated risk of brain cancer, based on one case among 417 NRI-treated subjects during 14.6 years of follow-up. Radiation doses to the brain were not presented in their report; however, the maximum radiation dose to the pituitary gland in the youngest children was 18-36 cGy [33], which is comparable to our study (range, 1-59 cGy), but lower than reported for the youngest children in the Maryland study (78 to 170 cGy) [15]. A follow-up study of 1,214 adult submariners treated with NRI 50 years earlier resulted in a slightly elevated, non-significant risk of fatal head and neck malignancies (RR=1.47, 95% CI: 0.61 to 3.50) but brain cancer risk was not specified [14].

Elevated risk of intracranial tumors (malignant and/or benign brain tumors) was reported after treatments for benign head and neck conditions, such as tinea capitis with external X-rays [1,37], but brain doses (> 1 Gy) were higher than in our cohort. A study of 28,008 infants

treated for haemangioma suggested an elevated risk of intracranial tumors at mean brain dose of 7 cGy, although significantly elevated SIRs were only seen in subjects exposed to more than 10 cGy (up to 11 Gy), and risk was highest among those exposed before 6 months of age [2]. We did not observe any benign brain tumors in our exposed group, although two cases of undetermined type were identified from death certificates. We limited analysis to malignant brain tumors because The Netherlands cancer registry has not collected data on other intracranial tumors. Although there is no evidence of elevated risk for brain tumors in The Netherlands NRI-exposed population so far, mixed results hamper any definitive conclusion on NRI-associated brain tumor risk at present.

We observed an overall two-fold increased risk hematopoietic and lymphoproliferative malignancies. Other NRI cohorts [14,15,33] do not show this and we found no evidence of a dose response. Radiation-associated excess risk of leukemia is well-documented [38,39]. However, with NRI, total ABM doses were low (0-3 cGy) and even doses to the ABM in the head and neck area (i.e., close to the nasopharynx) did not exceed 10 cGy. Evidence linking radiation to multiple myeloma is controversial [38]; although all four cases of multiple myeloma in our cohort were observed among the more heavily exposed subjects, the meaning of this finding for NRI-related cancer risk is unclear.

NHL is usually considered not to be related to radiation [38,40]. Although we found a 2.3-fold elevated risk of NHL among exposed subjects, evidence of a dose-response relationship was lacking even though the radiation dose to lymphoid tissues in close vicinity of the pharynx, such as the tonsils, was much higher than the total ABM dose (averaging 21 cGy, ranging up to 130 cGy). Similar results regarding NHL risk were obtained from an analysis of cancer mortality in this cohort [18]; it should be noted, however, that 7 out of 12 incident (exposed) cases represent subjects who died from NHL. Therefore, the findings are not entirely independent.

Non-significantly elevated risk of subsequent NHL has been reported among patients with pharyngeal carcinoma, based on data from the Connecticut (1935-1982; O=4; SIR=2.2) [41] and Danish cancer registries (O=3; SIR=3.2) [42]. Pharyngeal tumors are predominantly treated with radiotherapy, both locally and at the cervical lymph nodes [43]. Of twelve exposed cases, in our study two lymphomas first presented at the cervical lymph nodes, another in the parotid salivary gland and one in the tonsillar region. Although the observation of otherwise rare parotid and tonsillar NHL cases is remarkable, we found statistically non-significantly elevated SIRs for NHL in all areas of the body.

Alternatively, other risk factors for NHL among NRI-treated subjects may play a role. Liaw et al (1997) reported on elevated risk of lymphoma after tonsillectomy and speculated on the involvement of altered immune function after tonsillectomy (with or without adenoidectomy) in early childhood and simultaneous exposure to viruses associated with tonsillitis (such as EBV)

[44]. We recognize that our finding of elevated NHL risk is remarkable, as the lymphoproliferative system was involved in the indication for NRI and the malignancy of interest. In view of the literature on radiation-induced malignancies, the lack of confirmation from other NRI cohorts and the small numbers of cases in studies that do find an association (including ours), our finding may be explained by chance alone.

Recently, Yeh et al [15] reported a 60 percent decrease in the risk of sex-hormone related cancers, defined as breast, ovarian, endometrial and prostate cancer, in the Maryland cohort. The authors hypothesized that the observed deficit might be associated with radiation damage to the pituitary gland and subsequent decreased levels of circulating sex hormones. In our study, the risk of female genital tract malignancies was nonsignificantly decreased, but mainly due to a deficit of cervical cancers, a malignancy known to have a strong viral rather than hormonal etiology [45].

In contrast, we demonstrated a (statistically significant) 1.5-fold increased risk of breast cancer, in agreement with our previous evaluation of cancer mortality [18]. An analysis restricted to non-fatal breast cancer cases (65 percent of all breast cancer cases) also showed an elevated SIR, i.e., mortality and incidence analyses of our cohort provided independent results. Breast cancer risk increased in the later parts of the follow-up and among subjects treated between the ages of five and fourteen, a critical time-window for tumor induction in breast tissue [38].

There was also evidence of a breast cancer dose-response relationship, with an ERR per cGy of 4.8, which would correspond to an ERR *per gray* of 480, under linearity assumptions. UNSCEAR [38] however reported estimates of excess risk at 1 Gy in the order of 0.35 to 3.32 for three cohorts exposed to radiation during childhood. Because of the huge discrepancy between our result and the relatively homogenous findings from the UNSCEAR review, we consider that the breast cancer excess we observed may be due to chance. In any case, our study does not confirm the deficit of hormone-related cancers reported for the Maryland cohort [15].

The results of this study should be viewed in light of some methodological concerns. Despite the long follow-up and relatively large cohort size, case numbers are small and consequently risk estimates have wide confidence intervals. The possibility of chance findings should therefore be considered for each of the estimates.

In the general population comparison (SIR-analysis) selective refusal and incompleteness of case-finding before 1989 are potential sources of bias. Among non-responders, we have no information on case-status before 1989. From the NCR linkage (1989-1996) we know, however, that in the exposed group, the SIR for total cancer among non-responders was only slightly higher (6 observed cases, SIR=0.7) compared to the SIR among participants (29 observed cases, SIR=0.5). Non-fatal tumors that occurred among decedents before 1989 also will have been missed. As only 6 percent of all subjects had died as of 1997, it is unlikely that this potential loss

of information seriously affected our findings. An analysis restricted to cancer cases ascertained through cancer registry linkage, i.e., after 1989 only, showed results comparable to our main findings. Among survey participants, medical file abstracts were retrieved for 45 percent of all 'cancer-suspect' questionnaire answers. Among all medically confirmed diagnoses, only 11 percent concerned a malignant tumor. We reported on the validity of self-report compared to the NCR linkage elsewhere [46].

In the internal comparison (RR-analysis) we assumed incompleteness in case finding to be non-differential by exposure status. Death rates, tumor confirmation rates and cancer rates (1989-1996) among non-responders were indeed comparable for exposed and non-exposed subjects. However, the refusal rate was slightly higher among non-exposed subjects. As disease status of refusers and motives for refusal were unknown, we cannot exclude the possibility of differential refusal by disease status. On the other hand, our risk estimates based on cancer incidence compared well with the cancer mortality findings [18] which are unaffected by selective participation.

We chose to include multiple primaries in the analyses, because NCR reference data also include multiple primaries. Since second malignancies can be associated with treatment for a first cancer [47], we repeated analyses including first primaries only; although risk estimates were slightly reduced, main conclusions were by no means altered.

Strong features of the design include the availability of individual treatment records, a reasonably complete follow-up (92%) for both exposed and non-exposed subjects, the availability of an internal comparison group of non-exposed subjects and the large size of the cohort compared to any of the earlier studies.

In conclusion, these data provide little evidence for a high excess risk of cancer following NRI treatment. Inconsistent findings across studies and public concern warrant further prolonged follow-up of available cohorts.

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5

Assessment of cancer incidence from health questionnaire data: a validation study

Summary

The authors assessed accuracy of self-reported cancer occurrences, with and without medical verification, against cancer registry linkage in a Dutch cohort of patients treated 19-50 years earlier for ear-nose-throat conditions. In 1997, 6,528 subjects (mean age 41 years) participated in a questionnaire survey aimed at capturing all potential cancer cases. Four items, on tumors/growths, hospital admissions, biopsies, and radiotherapy, were used as clues to identify possible cases. Self-reported diagnoses were author-classified as probably benign, probably malignant, or uncertain with regard to type of disorder. After written consent, medical verification was sought for diagnoses classified as probably malignant or uncertain. Linkage with The Netherlands Cancer Registry revealed 55 invasive tumors (1989-1996). As expected, positive predictive value (PPV) of self-report itself, without investigator input, was poor. However, for self-reported diagnoses that had been author-classified as probably malignant (N=65), sensitivity was 0.78 and PPV was 0.66. The PPV rose to 0.91 for medically verified cases (N=43); seven of 12 false-negative cases were due to failure to obtain verification-consent. Women reported better than men. The study showed that self-reported diagnoses, including investigator-interpretation and medical verification, resulted in a high PPV and a reasonably high sensitivity for most tumors in a not particularly health-conscious population.

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Introduction

Mailed questionnaires can be used in large-scale epidemiologic follow-up studies to assess cancer incidence or prevalence rates, for example when a cancer registry is not (yet) available, when study resources are insufficient to allow for in-person interview strategies or when access to medical records is not readily available. Until recently, few settings allowed for the potential to study the value of methods relying on self-reported tumors, relative to either medical record information [1-4] or cancer registry linkage [5-10] (Table 5.1). We had the opportunity to assess the accuracy of self-reported and subsequently medically verified cancer occurrences against cancer registry linkage in a Dutch cohort of patients who had been treated for (mainly childhood) head and neck conditions 19-50 years earlier. In contrast to most of the earlier studies, this population covers a wide age range [3,4,6] and is not atypical of the general (Dutch) population in terms of education level or health consciousness [2,3,7,8].

Materials and Methods

Study population and ascertainment of outcome

We conducted a retrospective cohort study to examine late health effects of nasopharyngeal radium irradiation in The Netherlands. This now abandoned treatment was widely used to treat chronic ear conditions among children and in the military [11,12]. Detailed methods have been described elsewhere [13]. In brief, 5,358 exposed and 5,265 non-exposed patients were identified and followed until September 1997. All subjects had been treated by an ear-nose-throat physician between 1945 and 1981. Median age at treatment was 6.5 years; 90 percent of all subjects were younger than 20 years old at treatment. In 1997, median follow-up reached 30 years.

The main outcome, cancer incidence, was assessed through linkage with the nationwide Netherlands Cancer Registry, which was established in 1989. As the majority of subjects entered our cohort between 1950 and 1970, however, the registry data only covered a small part of the entire follow-up period. Therefore, we conducted a parallel case finding method by means of a questionnaire survey, including medical verification of potential cases, among all subjects known to be alive in September 1997 (N=9,142). For the eight years between 1989 and 1996

Table 5.1
Overview of published studies on accuracy of self-reported cancer diagnoses, for total cancer, and selected sites*

Reference	type of population	population size	method of self-report	gold standard	tumor sites	No. of true cases	sensi-tivity	PPV	remarks
Madow, 1973 [1]	population-based M+F; age 17-65+ y	†	in-person interview	Phys	all sites	49	0.61	0.53	Covers 1 year only
Colditz et al, 1986 [2]	nurses, F; age 30-55 y	121,700	self-administered questionnaire	Med Path	large bowel breast	‡		0.78 0.92	
Paganini-Hill & Chao, 1993 [3]	elderly, well to do, health conscious	13,897	postal survey: 1. cancer told by doctor 2. specify site & year 3. ever hospitalized?	 Med Path	§all sites colon breast prostate	327 ¶ 55 69 56	0.83 0.89 0.90 0.59	0.95 0.77 1.00 0.94	beneficial effect of combining answers to tumor and hospital admission questions
Kehoe et al, 1994 [4]	case-control; M+F; average age 65 y.	942	in-person interview	Phys	all sites	86	0.71	0.41	physician reports not complete for all subjects
Schrijvers et al, 1994 [5]	cross-sectional; M+F; age 15-74 y;	17,940	postal survey; cancer (yes/no)	CR	§all sites	348	0.67	0.66	overestimation prevalence; men vs. women; old vs. young and urban vs. rural
Berthier et al, 1997 [6]	cross-sectional; M+F; age 75+ y	3,349	postal survey, question on type and site of tumor	CR	§all sites prostate	291 97	0.21 0.16	0.77 0.83	women better than men
Bergmann et al, 1998 [7]	Cancer Prevention Study; M+F; age 39-96 y; educated, health-conscious	65,582	questionnaire: 1. ever physician-diagnosed cancer? 2. tumor sites + year	CR	§all sites colon breast prostate	3,314 # # #	0.79** 0.85 0.91 0.90	0.75 0.54 0.85 0.80	sensitivity<: age 70+ years, current smokers, lower education
Kato et al, 1999 [8]	F, age 34-65 y; motivated	12,947	self-adm questionnaire + med. record verification	CR	breast	242	0.79	0.76	NB includes non-responders to the questionnaire survey !
Kliewer, 2000 [9]	Cross-sectional; M+F; age 40-80 y	10,578	self-report	CR	all sites		0.21	0.91	
Desai et al, 2001 [10]	Population sample M+F; age 18-85+ y	5,034	self-report ; have you ever had cancer? (yes/no)	CR	all sites colon breast prostate	263 38 53 19	0.61 0.58 0.79 0.58	-	includes cancer diagnoses up to 45 years before interview ; focus on negative predictive value

* M= males; F= females; y= years; Phys= physcian; Med= medical record; Path= Pathology Record; CR= Cancer Registry linkage; PPV= positive predictive value;
† sample size unknown; total number of subjects with reported condition either on physician report or questionnaire = 5,027;
‡ true number of cases (and thus sensitivity) unknown as self-reports are verified by pathology report; no independent source of case finding was used; positive predictive value is based on confirmation rate among all self-reported cases (for some a medical record could not be obtained);
§ excluding non-melanoma skin cancer;
¶ results mentioned refer to first follow-up round only;
# site-specific true numbers of cases not given;
** exact match of tumor site and diagnosis date within one year of actual date.

information on cancer incidence from both sources was available. Present analyses were restricted to subjects who returned a completed questionnaire.

The Netherlands Cancer Registry

The Netherlands Cancer Registry comprises nine regional registries which periodically receive lists of newly diagnosed cases from a database of Pathology reports (PALGA). In addition, lists of hospitalized cancer patients are obtained from all hospitals and radiotherapy institutes in the specific region. Trained registration clerks frequently visit each hospital for retrieval of listed medical files and/or pathology reports. Tumor information from the medical records is coded according to the International Classification of Oncology and subsequently stored in the regional cancer registry's database. Both invasive and in-situ malignancies are registered, with the exception of basal cell carcinoma of the skin and cervical in situ lesions [14-17]. Completeness of the registry has been reported to be as high as 96 percent [14,15]. For our study, codes according to the International Classification of Oncology were converted to the 9th revision of the International Classification of Diseases (ICD-9) by the cancer registry.

Questionnaire Survey

The questionnaire survey consisted of two mailings followed by a telephone survey, two months after the first mailing, of non-responders. In all, 6,528 subjects returned a completed questionnaire resulting in a participation rate (among those alive) of 71 percent. Among participants, 94 percent were between 20 and 59 years old and only six percent were older than 60 years (mean age 42). There were slightly more males (54 percent) than females.

The questionnaire was intended to retrieve information on the occurrence of benign tumors, in situ lesions and invasive cancers. As it is known that patients do not always distinguish accurately between these different forms of neoplasia [2], and because the Dutch medical system offers good opportunities to obtain verified information from medical records, the questionnaire was designed to provide leads for this process. Four different questions were used to serve this purpose: (1) "Have you ever been diagnosed with a tumor (benign or malignant) or cancer of one of the below-mentioned organs or tissues? If yes, please indicate how old you were at that time, or in which year the diagnosis took place". Sites and cancers itemized were specific organs/tissues of the upper body (that might conceivably receive non-trivial doses from a

nasopharyngeal radium implant), the reproductive organs, and leukemia and lymphoma, plus "other"; subjects were instructed to answer "yes" or "no" for each item. (2) The second question was "Have you ever been admitted to hospital ? If yes, please indicate year, reason for admission and name of the hospital". Questions (3) and (4) concerned biopsies and radiation treatments, respectively, and respondents were asked for information on indication, or organ involved, and for calendar year of treatment.

All questionnaires were reviewed manually to select subjects with at least one affirmative answer to these four questions. In case the selected answer (or combination of answers) was judged to be related to a specific non-tumor diagnosis, no further action was taken. All questionnaires that indicated the possibility of a tumor or growth were classified by one of the authors (CMR) as "probably benign", "probably malignant", or "uncertain" (i.e., as to malignancy).

All subjects with diagnoses judged to be probably malignant or uncertain were contacted again for the identity and address of the relevant physician or hospital, and written permission to contact them. With subjects' consent, the physicians concerned were requested to provide pathology reports or, if not available, patient discharge letters or other correspondence in which a description of the diagnosis and the year of occurrence of the disease as reported by the participant were clearly stated. Tumor diagnoses were coded according to ICD-9 by two of the authors (CMR and PGV) working independently. Discrepant outcomes and complex tumors/ diagnoses were discussed with a professional and experienced coding assistant at the regional Comprehensive Cancer Center (IKL), to ensure appropriate coding.

Analysis

In general, cases of cancer were defined as invasive tumors (ICD9-codes 140-208) excluding non-melanoma skin cancers (ICD9-code 173) and metastases (ICD9-codes 196-198). Although the questionnaire survey covered over three decades, present analyses were restricted to self-reported cases with questionnaire-based years of diagnosis between 1989 and 1996, i.e., the time-window in which cancer registry linkage results were available. Within this frame we explored six different approaches (A-D, below) to classify cases and non-cases based on the questionnaire information, with or without coding of suspicious diagnoses and/or medical verification.

The number of cases ascertained by each method was then compared with the cancer registry linkage result (gold standard). Each method was evaluated in terms of sensitivity,

defined as the proportion of correctly classified cases among all cases according to the gold standard, and positive predictive value (PPV), defined as the proportion of correctly classified cases among all cases.

Figure 5.1 provides a schematic overview of case-finding procedures originating from self-reported diagnoses in the questionnaire survey. In addition, the lower part of the figure shows the extent to which the information from the different procedures was incorporated in the 6 different approaches to case definition. The A-Methods assessed the value of self-report only. With Method A1, any subject with an affirmative answer to the tumor question was defined as a case, whereas in Method A2, only subjects who mentioned the same tissue or organs both the tumor item and the hospital admissions item were defined as cases. Similarly, for Method A3 designation as a case required affirmative answers to both the tumor question and the biopsy item and Methods A4 required affirmative answers to both the tumor question and the radiotherapy question.

Method B was based on single affirmative answers, or combinations of affirmative answers, that had been author-classified as probably malignant or uncertain. As information from the medical verification was not taken into account, Method B was not conditional upon participants' consent or physician cooperation, in contrast to Method C. Method C represented our main approach to be tested, with cases defined as only those self-reported diagnoses that were medically verified to be malignant tumors.

An alternative approach, Method D, combined characteristics of methods B and C in as such that all verified self-reported tumors were considered as cases, as in Method C. In addition, however, probably malignant diagnoses for which medical verification could not be obtained, were also defined as cases in Method D. The latter method was not a priori defined but conceived on the basis of the inability to obtain medical verification for a number of probably malignant self-reported diagnoses.

To estimate the number of tumors that we missed by using combined information from the cancer registry linkage and our standard definition of self-reported tumors (Method C), a capture-recapture analysis as described by Hook and Regal [18] was performed.

Figure 5.1
Overview of information-use from several study procedures in 6 different case classification methods, originating from self-report

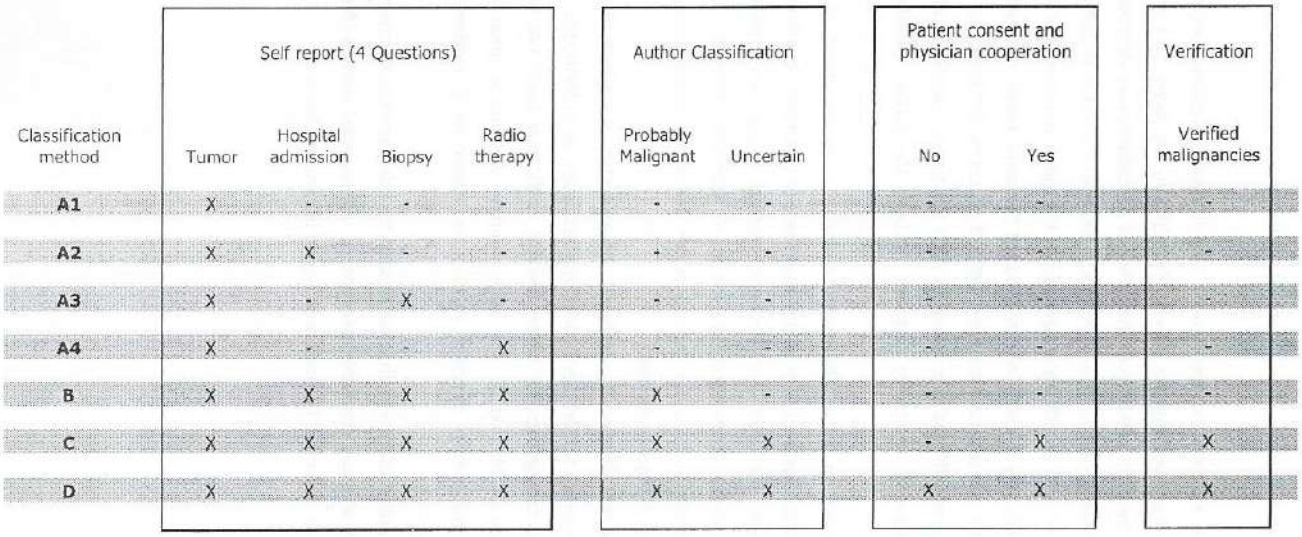

Table 5.2
Validity characteristics of various methods to classify cancer cases based on self-report, with or without coding of suspicious diagnoses, and with or without medical verification, against results of linkage with The Netherlands Cancer Registry (1989-1996) among participants of the Radium Cohort study

			linkage with The Netherlands Cancer Registry (gold standard)*				
method	definition of a case of cancer based on the questionnaire survey	all reported cases	true positive	false-positive	false-negative	sensitivity	positive predictive value
A1	affirmative answer tumor question (irrespective of other answers)	313	45	268	10	0.82	0.14
A2	affirmative answer tumor + hospital admission question	131	37	94	18	0.67	0.28
A3	affirmative answer tumor + biopsy question	169	29	140	26	0.53	0.17
A4	affirmative answer tumor + radiotherapy question	31	23	8	32	0.42	0.74
B	self-reported diagnosis, author-classified as probably malignant (no medical verification)	65	43	22	12	0.78	0.66
C	self-report and medical verification	47	43	4	12	0.78	0.91
D	self-report and medical verification OR self-report and probably malignant diagnosis but failure to verify due to lack of consent	55	49	6	6	0.89	0.89

* N=55 invasive tumor occurrences according to cancer registry linkage among 6528 participants

Results

The linkage with The Netherlands Cancer Registry revealed 55 invasive tumors among 6,528 participants. Table 5.2 shows the results of six different approaches of case definition based on the questionnaire survey, with or without further information.

Method A1, which relied on the tumor question only, had a sensitivity of 0.82 based on 45 correctly identified cases, but the PPV was only 0.14. The combination of affirmative answers to both the tumor and the hospital admission questions (Method A2) decreased sensitivity to 0.67 and elevated the PPV slightly, whereas the combination of affirmative answers to the tumor and biopsy questions (Method A3) did worse with regard to both sensitivity and PPV. Method A4, including information from the radiotherapy item also had a low sensitivity, but the best PPV of methods presented so far (Table 5.2).

For case-definition according to Method B, information from the author-classification was required. From the total number of 946 self-reported diagnoses (restricted to years of diagnosis 1989-1996) more than 60% were author-classified as uncertain. According to method B, all 65 diagnoses that had been author-classified as probably malignant were defined as cases. Table 5.2 shows that among them, 43 were confirmed in the cancer registry linkage. The sensitivity of method B against the cancer registry was 0.78 and the PPV was 0.66.

In Method C, only medically verified malignant tumors qualified as cases. Note the contrast to Method B, as medical verification was not only sought for probably malignant cases, but also for cases that were author-classified as uncertain. In all, 43 cases were correctly identified through self-report and subsequent verification, rendering a sensitivity of 0.78. Of the 12 cases that were missed by this method (false-negatives), eight had been classified as uncertain or probably malignant based on questionnaire information, but medical verification was not possible due to inability to obtain the participants' consent (N=7), or because we failed to contact the physician (N=1). For the other four missed cases, medical verification had not been sought because they were author-classified as probably benign (see tumor-specific results).

Four false-positive cases were in situ tumors according to the cancer registry but had been classified as invasive tumors by the project team based on available medical file information from the verification procedure. In one case, medical information provided by the physician turned out to be incomplete. In three other cases (a kidney tumor and a bladder tumor in one subject, and a stomach tumor in another subject) we had overlooked statements as to the non-invasiveness of the tumors in the respective pathology reports. The PPV was thus 43/(43+4)=0.91.

Of 43 correctly classified cases according to Method C, 31 were reported in both the tumor and the hospital admission question, and only four tumors were exclusively mentioned in the tumor question, without affirmative answers to one of the other three items. Furthermore, only three self-reported calendar-years of diagnosis deviated from the date reported by the cancer registry (and medical record), and then by one year only. As mentioned earlier, there were eight "probably malignant" diagnoses that could not be verified due to lack of consent or physician cooperation. We decided to combine information from methods B and C, by including these eight diagnoses as cases (Method D). Six of eight diagnoses were confirmed to be malignant tumors in the cancer registry, thus, for method D the number of true positive cases rose from 43 to 49 and the number of false-positive cases rose from four to six, rendering a sensitivity of 0.89 and a PPV of 0.89.

Table 5.3 shows validity characteristics by sex and exposure status, using standard Method C. Females scored higher on sensitivity and PPV than males. Exposure status had no major influence on validity characteristics.

In the above-described evaluation of the validity of self-reported tumors, the cancer registry was regarded as the "gold standard." However, the questionnaire survey and subsequent medical verification procedure revealed four additional cases that were not reported by the cancer registry. These cases were not considered in the analyses presented so far. One case (non-Hodgkin's lymphoma) was missed due to a misspelled family name and two cases (melanoma and breast cancer) were registered years after the initial date of diagnosis, i.e., after the linkage procedure for our study took place. It is unknown why the fourth case (breast cancer) did not appear on the linkage result file as all data were correct and the case had been reported to the nationwide database. Based on our findings, completeness of the linkage with the cancer registry was 55/59 = 92%.

Table 5.3
Validity characteristics of medically verified self-reports versus cancer registry by gender and exposure status in the radium cohort study (1989-1996)

	No. cases Cancer registry	Sensitivity	PPV
Gender			
Male	17	0.65	0.79
Female	38	0.84	0.97
Radiation treatment			
Yes	31	0.81	0.89
No	24	0.75	0.95

Table 5.4
Capture-recapture analysis for assessment of cancer occurrence based on self-report and medical verification (Method C) versus linkage with the Cancer Registry *

		cancer registry linkage	
		Yes	No
Self-report & medical verification	Yes	43	4
	No	12	x

*Estimated number of cases missed by both methods: x = bc/a (4 x 12)/43 = 1.1
Estimate of completeness of combined methods: (a+b+c)/(a+b+c+x) = 0.98

Taking the above four cases into account we conducted a capture-recapture analysis to estimate completeness of the entire process of cancer incidence assessment using information from both self-report followed by medical verification and cancer registry linkage (Table 5.4). For invasive tumors, one case was missed by both methods, rendering a completeness of 0.98 for the period under study in the presented analyses.

Discussion

We validated an approach to assess cancer incidence based on self-report and subsequent medical verification against linkage with the cancer registry, in a cohort that covers a wide range of age, level of education and health-consciousness. Based on four questions regarding tumor occurrence, and permission for verification, 78 percent of true cases according to the cancer registry were correctly classified. Schrijvers et al [5] reported a sensitivity of 0.67 for self-report only in another Dutch population, whereas sensitivities around 0.8 were reported for self-report in educated and health conscious populations [3,7]. Recently, Desai et al [10] described a sensitivity of 0.61 in a community-based cohort. In their study, self-report was based on a general question on cancer only and cases diagnosed up to 45 years earlier were included (see also Table 5.1).

Most false-negative cases in our study resulted from failure to obtain permission to contact a physician. When the verification phase was not considered, and definition of a case was either based on self-report classified to be suspect for malignancy, or on an affirmative answer to the tumor question only, sensitivity remained at about 80 percent, but the positive predictive value dropped dramatically. Although Paganini-Hill & Chao [3] reported increased sensitivity after adding an item on hospital admissions to a tumor question, our study does not confirm their

result. It should be noted, that our questionnaire was solely intended to serve as a rough selection tool to identify participants possibly suffering from cancer, with the intent to minimize the occurrence of false-negative reporting of cancer. As a consequence, conclusions regarding the validity of the tumor question only, or in combination with the hospital admission and the biopsy questions, cannot be generalized easily.

In addition, the tumor question specifically listed organs in the upper body only. We speculate that not naming specific organs might have influenced false-negative reporting of tumors of lower body parts, such as prostate and colon cancer. However, other studies showed mixed results with regard to validity of self-reports for these tumors, with a low sensitivity for prostate cancer in elderly populations [3,6]. For colon cancer PPVs between 0.5 and 0.8 have been reported [2,3,7]. In view of small number of site-specific cases, we quantified validity of self-reported breasts cancers only. Breast cancer is known to be well reported across populations [2,3,7,10] except for the very elderly [6]. In our study sensitivity was 0.84, as three probably malignant cases could not be verified. Kato et al [8] reported a sensitivity of 0.79 in a design very similar to our study although their registry linkage included subjects lost to follow-up.

Among several case-classification methods, overall sensitivity in our study was highest for an unconventional approach, which combined verified cases with those non-verified that had been labelled as "probably malignant" by the authors. As this method (D) was mainly data-driven, we are cautious in recommending it. On the other hand, it is plausible that studies among (presumed) cancer patients another settings also suffer from the inability to obtain consent to verify suspect cases as fail to obtain consent in a number of cases as this problem seemed to be related to severity of illness in our study.

The CR linkage was regarded as the gold standard throughout this report; however, the occurrence of unidentified cases of invasive cancer showed that this method is not a complete source of information. The number of missed cases was small (N=4) and did not seem to be related to relevant study factors. In three of four missed cases, lack of identification was caused by factors related to timing and practice of the linkage procedure itself. Available personal identifiers in our study could have been prone to spelling errors, thereby slightly reducing the linkage effectiveness, as was demonstrated by the one case missed for this reason. Unlike many of the other validation studies, migration outside the coverage area of the registry or loss to follow-up cannot explain missed cases5-8,10 as all eligible subjects were known to be alive and resident in the Netherlands at time of linkage, and the CR has nationwide coverage [15].

As to completeness of coverage of the CR itself, it is known that cancer patients without pathology confirmation who are treated ambulatory, or by the general physician only, are systematically missed by the Netherlands Cancer Registry [15]. We found no such cases in our participants group, but cannot exclude the possibility of selective non-response of the very

elderly or terminally ill in this particular group and thus lack of coverage of both case-finding methods. Combining earlier published data on completeness (96 percent) and linkage success (98 percent) in one region, the maximum success rate for any given linkage would be 94 percent [14,15], which is comparable to our finding of 92 percent completeness.

In conclusion, our study showed that self-report of tumors, classification of probably malignant or uncertain diagnoses and subsequent medical verification resulted in high positive predictive values and reasonably high sensitivity in a population of average educational background and health consciousness. When applying this approach, sufficient effort should be dedicated to achieving consent for medical verification, as the sensitivity depended heavily on the opportunity to retrieve medical records.

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6

Late health effects of childhood nasopharyngeal radium irradiation: non-melanoma skin cancers, benign tumors and hormonal disorders

Summary

Nasopharyngeal radium irradiation was widely used from 1940 through 1970 to treat otitis serosa in children and barotrauma in airmen and submariners. We assessed whether NRI-exposed individuals were at higher risk for benign tumors, non-melanoma skin cancer (NMSC), thyroid disorders, and conditions related to regulatory control of anterior pituitary hormones, such as growth and reproductive characteristics. We conducted a retrospective cohort study in 3440 NRI-exposed subjects and 3088 non-exposed subjects, who as children were treated at nine ear, nose and throat clinics in The Netherlands between 1945 and 1981. Based on information from original medical records we traced vital status through follow-up at municipal population registries. Disease status (including medical confirmation) and indicators of pituitary gland radiation damage were assessed from a self-administered questionnaire in 1997. The average radiation doses were 11, 7 and 1.5 cGy for pituitary, parotid, and thyroid gland, respectively. Among exposed subjects, 23 benign head and neck tumors were observed, compared to 21 among non-exposed subjects. Elevated risk of basal cell carcinoma (BCC) of the head and neck area was observed in exposed subjects (OR = 2.6, 95% confidence interval (CI): 1.0-7.2). Exposed and non-exposed groups did not differ substantially with regard to thyroid disorders, height and reproductive characteristics, although exposed males more frequently reported a history of subfertility compared to non-exposed males (OR=1.4, 95% CI: 1.0-2.1). We found no evidence of highly elevated risk of benign head and neck tumors, NMSC, thyroid disorders or indicators of pituitary radiation damage, following childhood nasopharyngeal radium irradiation in The Netherlands.

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Introduction

From the early 1940s until 1960 nasopharyngeal radium irradiation (NRI) was regarded as a safe and effective treatment for (childhood) otitis serosa [1-4] and barotrauma (aerotitis media) in military submariners and airmen [5,6]. These conditions are characterized by lymphoid hyperplasia in the nasopharynx, causing impaired Eustachian tube functioning, hearing loss and pain. In the late 1920s, Dr SJ Crowe developed a small radium applicator attached to a pin that could be inserted through the nostrils into the nasopharynx, where the radium exerted its activity on the local overflow of lymphoid tissue [1,2]. NRI was used in several European countries, the US and Canada [7,8]. The Centers for Disease Control and Prevention has estimated that between 0.5 and 2 million children were treated with NRI in the US, as well as 8,000 military submariners and aviators [7].

Following childhood radiation exposure, elevated risks of benign head and neck tumors and non-melanoma skin cancers (NMSC) have been reported [9-12], as well as benign radiation-related disorders of the thyroid, e.g., nodular disease and hypothyroidism [13,14]. In NRI, the pituitary gland receives relatively high doses of γ-radiation (range, 0.01-0.59 Gy) compared to other head and neck organs [15] because of its close proximity to the treatment areas in the nasopharynx [16]. If NRI results in damage to the pituitary gland, this might affect circulating hormone levels [17,18], growth and reproductive characteristics, e.g., early menarche, fertility disorders and early menopause, as has been observed among cancer patients who were treated with high-dose (20-70 Gy) cranial radiotherapy at childhood ages [19-21]. So far, only scarce data are available on the occurrence of disorders other than cancer among NRI-exposed populations [8,22].

In The Netherlands, NRI was introduced after WW-II and was used widely until the early 1970s [8]. We retrospectively traced original radiation treatment records of 5,358 patients. In previous reports we described mortality [15] and cancer incidence [23] in this population. The present report describes NMSC and non-malignant disorders possibly associated with NRI exposure.

Methods

Study population and data-collection

Building on a previous study [24] we defined an expanded cohort of 5,358 NRI-exposed and 5,265 non-exposed subjects. Non-exposed subjects were frequency-matched to the exposed group by clinic, sex, birth year and first consultation year. Non-exposed subjects had also been treated for ENT conditions, but had never been exposed to NRI. From the individual ENT treatment charts in the nine participating clinics, we recorded history of NRI (yes/no), a code for diagnosis at first consultation and, for exposed subjects, individual treatment characteristics including date and duration of each treatment session. Institutional review boards of all participating hospitals and research institutes approved the study protocol. Detailed descriptions of the definition of the cohort, data collection, follow-up and dosimetric methods have been reported elsewhere [15,23].

Radiation dosimetry

The clinics used different NRI-protocols with treatment conditions ranging from 3 to 76 mgh (mgh: mg radium times treatment duration in hours). Organ-specific doses were calculated based on simulations in age-appropriate, anthropometric phantoms, taking into account the distance from the radium applicator to the organ of interest [15,16]. Mean absorbed tissue doses (range) were as follows: nasopharynx: 275 cGy (32 to 1110), pituitary gland: 11 cGy (1 to 59), parotid gland: 7 cGy (1 to 28), thyroid gland: 1.5 cGy (0.2 to 11) and facial skin: 3.2 cGy (0.5 to 13).

Follow-up

Cohort members were traced through a search at municipal resident registries to determine vital status and address (if applicable) on September 15, 1997. For all subjects who remained untraceable, additional searches were done at the registry of emigrants and immigrants of the Dutch Ministry of Foreign Affairs and at the Central Bureau of Genealogy, a nationwide registry of deceased Dutch citizens.

Health status assessment

We conducted a survey to assess health status, including cancer and non-cancer outcomes. A questionnaire accompanied by a letter of introduction from an ENT-physician of the hospital where the subject was treated, and an informed consent form were mailed to all living subjects in the cohort, as of 1997. Exposed and non-exposed subjects received identical letters, in which the purpose of the study was described as an evaluation of long-term health effects of several ENT treatments, including NRI. The study included a telephone survey of subjects who did not respond after two written requests. The questionnaire contained 43 items covering socio-demographic items, diseases known to be related to high-dose radiation to the head and neck area and possible confounders (occupation, smoking, alcohol consumption and exposure to various radiation sources).

The items on non-cancer outcomes were stated as follows: "Did you ever have any of the following conditions or diseases?" with checkboxes for yes / no / don't know. The outcomes of interest included thyroid disease, growth disorder, angina, otitis media, hearing loss, deafness, epilepsy, number of (biological) children, fertility problems and the diagnosed cause of subfertility (sperm disorder (males), obstruction of fallopian tubes (females), hormonal disorders, other cause, unknown or "prefer not to answer this question"). As we were interested in subfertility diagnosis of the participant only, and not in any such diagnoses of the participants' spouses, the question was asked for men and women separately, to allow for a crosscheck with the participant's gender. Among females we also assessed age at menarche (<12, 12-14, >14 years), number of miscarriages and age at last menstrual period. If the self-reported last menstrual period had taken place more than one year before questionnaire completion, and there was no mention of pregnancy or breast feeding at the time of questionnaire completion, the woman was considered to be post-menopausal. If the general remark section or the response concerning hospital admissions indicated a hysterectomy and/or oophorectomy we considered the woman to have had a "surgical menopause". Otherwise post-menopausal women were classified as having had "natural menopause".

In addition, four items (on tumors, biopsies, hospital admissions, and radiation therapy) were used to identify subjects who had ever suffered from a malignant or benign tumor, specified by organ or tissue. In an additional letter, subjects reporting a tumor were asked for the name of the treating physician and to complete a second consent form to allow release of medical data for study purposes. After consent was obtained, physicians were asked for copies of relevant correspondence or medical chart notes regarding the tumor or the underlying disease necessitating hospital admission, biopsy or radiation treatment. As the main focus was on

Table 6.1
Follow-up status in The Netherlands NRI cohort study

Follow-up status (as of Sept. 15th, 1997)	NRI-exposed No. (%)	Non-exposed No. (%)
Alive	4,624 (86)	4,518 (86)
Participation	3,440 (74)*	3,088 (68)*
Refusal	586 (13)*	728 (16)*
Non-response	598 (13)*	702 (16)*
Deceased	302 (6)	315 (6)
Emigrated	265 (5)	259 (5)
Lost to follow-up	167 (3)	173 (3)
Overall	5,358	5,265

* percentage of total number of subjects eligible for the questionnaire survey (i.e., alive)

disorders of the head and neck area, we did not seek medical confirmation for skin lesions known to be located below the diaphragm or on the extremities. We applied a similar medical verification procedure for all subjects who reported a history of thyroid disease.

Definition of analytic cohort

From the total cohort of 10,623 subjects, 92 percent were traced, of whom 617 had died and 9,142 were alive with known addresses. In all, 3,440 (74 percent) exposed and 3,088 (68 percent) non-exposed subjects participated in the survey and were thus eligible for the present analyses (Table 6.1). Analyses of adult height and reproductive characteristics were restricted to subjects who were less than 10 years of age at time of ENT treatment (N=4,944, 76 percent of all participants), and would therefore be assumed not to have entered the pubertal growth spurt or, for female subjects, experienced menarche.

Data-analysis

The questions on ever having suffered from ENT disorders, epilepsy, hormonal, growth and thyroid disorders were grouped together in one section of the questionnaire. Descriptive analyses revealed that a considerable proportion of subjects had reported a history of one or two conditions, but had not completed the checkboxes for all other questions in this group. As a

result, we observed up to 20 percent of missing observations for some of these disorders. As the proportions of missing observations per disorder were very similar for exposed and non-exposed groups, we interpreted missing observations for these 10 questions to be a "no" if one or more of the other questions in this section was answered affirmatively. Subjects with missing responses for all 10 questions, i.e., 58 exposed (1.7 percent) and 72 non-exposed (2.3 percent) subjects, were excluded from analyses involving these 10 questions. Only disorders occurring after ENT-treatment were taken into account in the analyses.

Frequency tables of disorders of interest were assembled for exposed and non-exposed groups and homogeneity was tested using Pearson Chi-square tests [25]. Logistic regression models [26] were used to obtain odds ratios (OR) and 95 percent confidence intervals (CI) adjusted for gender, attained age and other possible confounders, as appropriate. Because the disorders/characteristics under study often showed non-linear associations with age, we modeled age at time of questionnaire survey as a categorical variable, <30, 30-39, 40-49, 50-59, 60-69 and ≥70 years, or <40, 40-49, 50-59 and ≥60 years, when sparse numbers of cases did not allow for finer stratification. Likelihood ratio tests for trend in radiation dose were performed by adding dose to the model as a single continuous variable. As adult height was normally distributed in our cohort, we used Student t-tests to compare the average adult height between the exposed and non-exposed groups.

Table 6.2
Population characteristics of The Netherlands NRI cohort by exposure status

	NRI-exposed group: No. (%)	Non-exposed group: No. (%)
Gender		
Male	1,861 (54)	1,674 (54)
Female	1,579 (46)	1,414 (46)
Age at first treatment (y)*		
0-4	749 (22)	1,336 (43)
5-9	1,869 (54)	990 (32)
10-14	454 (13)	353 (12)
15-19	115 (3)	159 (5)
≥ 20	253 (8)	250 (8)
Age in 1997 (y)		
<30	504 (15)	511 (16)
30-39	1,077 (31)	989 (32)
40-49	1,142 (33)	942 (31)
50-59	518 (15)	438 (14)
60-69	125 (4)	125 (4)
≥70	74 (2)	83 (3)

* date of first treatment refers to first radium treatment session among exposed and to first consultation among control subjects.

Results

The NRI-exposed and non-exposed subjects were comparable with regard to attained age (Table 6.2). The proportion of subjects treated before age five was greater among non-exposed compared to exposed subjects, because we matched the non-exposed group on calendar year of first consultation in the exposed group, rather than on calendar year of first radiation treatment. Among exposed subjects, the median age at treatment was 6.5 years and the median attained age was 40.9 years.

Table 6.3 shows the frequency of medically confirmed benign tumors in the head and neck area. Among exposed subjects, 23 benign head and neck tumors (excluding skin tumors) were observed, compared to 21 among non-exposed subjects. The number of tumors for each site of interest in the head and neck was small and equally distributed over exposed and non-

Table 6.3
Medically confirmed benign tumors and non-melanoma skin cancers among participants of The Netherlands NRI cohort study survey, by exposure status

Condition	ICD-9*	Number of cases: Exposed (N=3,440)	Number of cases: Non-exposed (N=3,088)	OR (95% CI)†
Benign head and neck tumors	210,(212-215).0-1, 224, 225.0-2, 226, 227.0-3	23	21	1.0 (0.5, 1.7)
Salivary glands	210.2	2	3	
Pituitary adenoma	227.3	1	1	
Thyroid gland	226	4	4	
Parathyroid gland	227.1	1	0	
Benign skin tumors‡	216	58	45	1.2 (0.8, 1.7)
Head neck area	216.0-4	24	19	1.1 (0.6, 2.1)
Other	216.5-9	34	26	1.2 (0.7, 1.9)
SCC of the skin	173	2	1	
Head neck area	173.0-4	2	0	
Other	173.5-9	0	1	
BCC of the skin‡#	173	19	14	1.3 (0.6, 2.6)
Head neck area	173.0-4	16	6	2.6 (1.0, 6.7)
Other	173.5-9	3	8	0.3 (0.1, 1.3)

OR odds ratio; SCC squamous cell carcinoma; BCC basal cell carcinoma
* international Classification of Diseases, 9th Revision [28]
† adjusted for attained age (<40, 40-49, 50-59, 60+ years) and gender; OR only estimated when at least ten cases were observed in the cohort
‡ only first skin tumors were included in analysis
# of 33 subjects with at least one BCC, 27 had one lesion, three subjects had two BCCs, one subject had three BCCs and one subject had four BCCs, not restriced to the head and neck area. In addition, one (exposed) subject had recurrent and multiple primary BCC and SCC lesions of the nose, jaw, cheek and parotid gland. In all, of six subjects with multiple lesions, two were exposed to NR.

exposed groups: in all, five benign salivary gland tumors, eight thyroid gland tumors and two pituitary adenomas were observed. The frequency of benign skin tumors of all body parts was also very similar for exposed and non-exposed subjects (Table 6.3). Among exposed subjects, only two squamous cell carcinomas of the skin (SCC), both of the lower lip, were observed, compared to one SCC of lower body parts in non-exposed subjects. The total number of basal cell carcinomas (BCC) was slightly higher among exposed subjects (OR=1.3), but the proportion of BCC located in the head and neck area was higher among exposed than among non-exposed subjects (84 percent vs. 43 percent, respectively (chi square p-value = 0.06). The risk of BCC restricted to the head and neck area was borderline significantly elevated (OR=2.6, 95% CI: 1.0 to 6.7). For other body parts, no excess was found (OR=0.3, 95% CI: 0.1 to 1.1). Among exposed subjects, we then compared the subgroup exposed to higher than median facial skin doses (> 2 cGy) (1187 subjects, 12 cases of head and neck BCC) to the group with median or lower skin doses (≤2 cGy, 2253 subjects, 4 cases) and found a slightly (statistically non-significant) elevated risk of head and neck BCC (OR=1.8, 95% CI: 0.5 to 6.1).

The data presented on skin tumors focused on medically confirmed cases. A total number of 615 subjects reported a history of potential skin tumors. Medical confirmation was not sought for 40 percent of all self-reported potential skin tumors, as these lesions were clearly benign, or concerned skin lesions of lower body parts. Among all subjects whom we asked for permission to medically verify the reported skin lesion, 84 percent of exposed and 77 percent of non-exposed subjects gave consent. The physician cooperation proportion was high, i.e., >95 percent in both exposure groups. Out of all self-reported cases for which physician cooperation was obtained, medical information was available in 80 percent of cases, and within that group, more than 70 percent concerned benign skin tumors or non-neoplastic skin disorders (approximately similar for exposed and non-exposed subjects).

With regard to non-neoplastic disease outcomes, we first assessed the reported frequency of thyroid disorders among exposed and non-exposed subjects (Table 6.4). Originally, 105 exposed and 81 non-exposed subjects reported a history of thyroid disease in the questionnaire. Consent for medical verification was obtained for 58 percent and 62 percent of exposed and non-exposed subjects, respectively. Forty-three benign thyroid disorders were confirmed among exposed subjects compared to 40 among non-exposed subjects (OR=1.0). Overall, there was no difference in the cumulative incidence of hypothyroidism. Among females, a history of nodular thyroid disease was more common among exposed subjects compared to non-exposed subjects (1.2 percent vs. 0.8 percent) but the difference was not statistically significant. The age- and sex-adjusted OR for nodular disease among exposed subjects was 1.3 (95% CI: CI 0.7 to 2.8). The OR for nodular disease among men vs. women was 0.1 (95% CI:

Table 6.4
Thyroid disorders among participants of The Netherlands NRI cohort study survey, by exposure status and gender

	Females only				Overall*				
	Exposed (N=1,579)		Non-exposed (N=1,414)		Exposed (N=3,440)		Non-exposed (N=3,088)		
	No.	%	No.	%	No.	%	No.	%	OR (95% CI)‡
Self-reported thyroid disorder†	75	4.7	62	4.4	105	3.1	81	2.6	1.2 (0.9, 1.6)
Medical verification possible?									
Consent obtained	47		41		61		50		
Physician cooperated¶	40		36		52		45		
Results of medical verification									
Benign thyroid disease $	34	2.2	33	2.3	43	1.3	40	1.3	1.0 (0.6, 1.5)
Nodular disease	19	1.2	11	0.8	20	0.6	13	0.4	1.4 (0.7, 2.7)
Thyrotoxicosis	6	0.4	7	0.5	11	0.3	10	0.3	1.0 (0.4, 1.8)
Graves' disease	2	0.1	4	0.3	5	0.2	5	0.2	0.9 (0.3, 3.0)
Hypothyroidism	4	0.3	6	0.4	5	0.2	6	0.2	0.8 (0.2, 2.5)
Other thyroid disorders #	3	0.2	1	0.1	4	0.1	1	0.0	#
Medical record incomplete	1		1		4		2		
No thyroid disorder	1	0.1	1	0.1	5	0.0	4	0.1	

OR = odds ratio, CI = confidence interval
* all p-values of the crude χ^2 test for exposure effect among males and females separately were >0.2 ; p-values only calculated if the expected frequency of all cells > 5.
† number of missing observations for this item: exposed group (58), non-exposed group (72).
‡ adjusted for attained age (<40, 40-49, 50-59, 60+ years) and gender; OR only estimated when at least 10 cases were observed in the cohort
¶ among the total of 97 (52+45) self-reported cases in which the physician intended to cooperate, there were six cases (four exposed, two non-exposed) in which the medical file was incomplete and did not contain data on thyroid disorders
$ includes International Classification of Diseases, 9th revision [28] codes 226 and 240-246.
# four thyroid cancers and one benign parathyroid tumor; risk estimates for malignant disorders (including cases ascertained from a cancer registry linkage procedure) have been reported elsewhere [23]

0.03 to 0.3). Additional adjustment for age at treatment did not affect the risk estimates for thyroid disease or nodular disease and there was no heterogeneity of risk across subgroups according to thyroid dose (not shown).

We assessed self-reported adult height (Table 6.5) and reproductive characteristics (Table 6.6) as indicators of possible radiation-related pituitary gland dysfunction among subjects younger than 10 years of age at time of treatment. Table 6.4 shows that height was almost identical when gender and age-specific exposed and non-exposed groups were compared. In the entire cohort, a clear trend of height with birth cohort was apparent. For example, among exposed males, average height increased from 178.9 cm among males older than 50 years in 1997, to 182.1 cm in the youngest group (<30 years). The right column of Table 6.5 shows age-specific self-reported height from a 1997 nation-wide population survey conducted by Statistics Netherlands among 22,344 Dutch citizens [27]. The trend related to birth cohort was similar and reported height was, on average, comparable, although both exposed and non-exposed males who were younger than 30 years of age in 1997 were slightly less tall than the reference population.

With regard to reproductive characteristics, exposed females were slightly more likely to have had children (OR=1.1) and to report a history of subfertility (OR=1.2) or miscarriages (OR=1.1), as compared to non-exposed females although the differences were very small and

Table 6.5
Adult height among participants of The Netherlands NRI cohort study survey who were treated before age 10 years, by gender, attained age and exposure status

		Exposed*		Non-exposed		General population survey†
Gender	Age as of 1997	No.#	Average (SE) height (cm)	No.#	Average (SE) height (cm)	Average (SE) height (cm)
Male	<30	278	182.1 (0.5)	265	181.9 (0.5)	183.5 (0.2)
	30-39	520	181.8 (0.3)	497	181.8 (0.3)	182.2 (0.2)
	40-49	496	180.5 (0.3)	366	180.2 (0.4)	180.4 (0.2)
	≥50	131	180.1 (0.6)	120	179.9 (0.5)	178.2 (0.2)
	All	1,425	181.3 (0.2)	1,229	181.1 (0.2)	
Female	<30	211	169.4 (0.4)	217	169.4 (0.4)	169.6 (0.2)
	30-39	416	168.0 (0.3)	388	168.1 (0.3)	168.7 (0.1)
	40-49	420	166.8 (0.3)	311	166.8 (0.3)	167.3 (0.1)
	≥50	120	167.3 (0.4)	125	166.6 (0.6)	166.2 (0.2)
	All	1,167	167.7 (0.2)	1,043	167.8 (0.2)	

* p-value (t-test exposed vs. unexposed) >.2 for all comparisons
# missing observation for adult height: exposed males (15), non-exposed males (20), exposed females (11), non-exposed females (14); excludes 3 non-exposed subjects 60-69 y of age
† self-reported height based on periodic population survey among 22,344 Dutch citizens by Statistics Netherlands [27]

Table 6.6
Reproductive characteristics and attained age among female participants of The Netherlands NRI cohort study survey, restricted to those treated before age 10

Characteristic*	Exposed (N=1178)‡ No.	(%)	Non-exposed (N =1057) ‡ No.	(%)	OR (95% CI) $
Attained age (years)					
<30	215	(18.3)	220	(20.8)	
30-39	418	(35.5)	391	(37.0)	
40-49	424	(36.0)	319	(30.2)	
≥50	121	(10.3)	127	(12.0)	
	P=0.02†				
Number of children					Ever vs. never
0	399	(34.0)	390	(35.8)	1.1 (0.9, 1.4)
1-2	611	(52.1)	537	(52.0)	
3-4	160	(13.6)	118	(11.6)	
>4	3	(0.3)	6	(0.6)	
	p=0.13				
History of subfertility					Ever vs. never
Never	1053	(90.8)	952	(92.3)	1.2 (0.9, 1.6)
tubal factor	21	(1.8)	17	(1.6)	
hormonal disorder	33	(2.8)	22	(2.1)	
other cause	30	(2.6)	17	(1.6)	
unknown cause	23	(2.0)	23	(2.2)	
	p=0.44				
Number of miscarriages					Ever vs. never
0	934	(81.0)	865	(82.7)	1.1 (0.9, 1.4)
1	167	(14.5)	130	(12.4)	
2	33	(2.9)	34	(3.3)	
3 or more	19	(1.6)	17	(1.6)	
	p=0.54				
Age at menarche (years)					<12 vs. older
<12	169	(14.6)	153	(14.7)	1.0 (0.8, 1.3)
12-14	823	(70.9)	716	(68.7)	> 14 vs. younger
>14	168	(14.5)	173	(16.6)	0.8 (0.7, 1.1)
	p=0.37				
Menopausal status #					Post vs. pre
pre menopausal	1003	(67.8)	894	(68.5)	1.0 (0.8, 1.3)
post menopausal	236	(15.9)	201	(15.4)	
Unknown	241	(16.3)	211	(16.2)	
	P=0.90				

OR = odds ratio, CI = confidence interval
* due to missing observations numbers do not always add up to total
† p-value of crude Chi-Square test for exposure effect
‡ mean attained age 38.6 yrs amonge exposed and 38.3 yrs among non-exposed subjects
$ OR for exposed compared to non-exposed adjusted for attained age (<30, 30-39, 40-49, 50-59, 60-69 and ≥70 yrs)
# analysis based on females first treated before age 20 (1,480 exposed and 1,306 non-exposed females).

statistically nonsignificant (Table 6.6). The number of reported miscarriages was equally distributed across exposure groups (Table 6.6).

Among males treated before the age of 10, the OR for having children was 0.8 (95% CI: 0.7, 1.0). Furthermore, among 1413 exposed males with available data, 72 (5.1%) reported a history of subfertility, vs. 44 (3.5%) among 1246 non-exposed males. The OR for a history of

subfertility among exposed vs non-exposed males treated before the age of 10 was 1.4 (95% CI: 1.0, 2.1). Analyses for a history of subfertility were then repeated by dose to the pituitary gland. Overall, there was a statistically significant trend of increasing risk with increasing pituitary dose (p=0.004) in males, which remained apparent when the non-exposed group was excluded (p=0.02). Compared to the non-exposed group the ORs for subfertility by tertiles of pituitary dose were 1.3, 1.1 and 1.8. Among females, there was no dose trend for subfertility (p>0.5), with ORs of 1.0, 1.3 and 1.0 by tertiles of pituitary dose.

The distribution of females over three categories of menarcheal age was similar among exposed and non-exposed subjects, with roughly 70 percent reporting ages of 12-14 years and 15 percent each in the categories of less than 12 years and older than 14 years at menarche, respectively (Table 6.6). In the subgroup of women younger than 20 years at first treatment, only 16 percent had reached menopause as of September 1997, and menopausal status was unknown in another 16 percent (Table 6.6). Exposed postmenopausal females were more likely (p-chi square=0.0001) than non-exposed females to have had a surgical menopause (32% and 16%, respectively). To address timing of menopause, we used the subset of 284 women who were treated by the ENT physician before age 20, were older than 40 years of age in 1997 and were postmenopausal at time of questionnaire completion. Of the 134 exposed and 150 non-exposed women, 29 percent and 30 percent, respectively, had reached menopause before age 45, and the average ages at menopause were 46.3 and 46.9 years, respectively.

Discussion

We assessed long term risk of non-cancer disorders and NMSC in the head and neck area after low-dose radiation exposures from NRI in The Netherlands. Main outcomes included benign tumors in the head and neck area, BCC, SCC, thyroid disorders, and conditions related to regulatory control of anterior pituitary hormones, such as growth and reproductive characteristics. No strongly elevated risks were demonstrated for any of the conditions we studied. The highest risk estimates were observed for head and neck BCC of the skin (OR=2.6), thyroid nodular disease (OR=1.4) and male subfertility (OR=1.4).

In contrast to findings reported after childhood head-and-neck X-ray treatments for thymic enlargement [11], tinea capitis [10] and enlarged tonsils [9] we did not observe an elevated risk of salivary gland tumors among NRI-exposed subjects. In the study by Schneider and others [9], a strong dose-response relationship was demonstrated at a dose range of 0.01 -

15.8 Gy (mean, 4.2 Gy, ERR =19.6; 95% CI: 0.16 to ∞). In our study, average dose to the parotid gland was only 0.07 Gy (maximum 0.28 Gy).

We further demonstrated a 2.6-fold borderline significant risk of medically confirmed BCC of the head and neck area. The average dose to the facial skin was 3.2 cGy. Long-term excess risk of BCC has been reported in several populations with skin doses of several gray from external radiation [29-32]. The relative risk of NMSC is thought to be inversely associated with age at exposure [33]. In the New York tinea capitis cohort, Shore and others [29] reported particularly increased risk of skin cancer among irradiated white subjects with light complexions, which led to the hypothesis of UV radiation as a cofactor for radiogenic NMSC. Their finding was not confirmed, however, in studies among atomic bomb survivors, although BCC was the major type of skin cancer associated with radiation dose in that population [31].

With NRI, appreciable skin radiation doses were only received by the facial skin, which is also commonly exposed to UV radiation. However, in our cohort, average dose to the facial skin was more than 10-fold lower compared to the tinea capitis studies [29,30]. It is tempting to speculate on NRI-induced BCC because we found some suggestion of elevated risk of head and neck BCC, mainly in subjects whose skin was exposed to the highest radiation dose. Also, 84 percent of all BCC among exposed subjects were found in the head and neck area, vs. 43 percent of BCCs in non-exposed subjects. However, a report from the Eindhoven Cancer Registry (1975-1988) showed that 81-84 percent of all BCC occurred in the head and neck area [34]. Similar proportions were reported by Holme and others [35] for repeated surveys conducted in South-Wales, i.e., 81 percent (1988 survey) and 75 percent (1998 survey). The agreement of the proportion of head and neck BCC in the exposed group with the population-based data renders an association with NRI less likely. Moreover, the observation may imply a deviant pattern among the non-exposed, which has pushed the OR for BCC of the head and neck area upwards. Bias or chance might explain this finding (see below). Only two SCC were observed among exposed subjects. Both SCC were tumors of the lower lip, which may be associated with sun-exposure and smoking [36]; the affected individuals were both heavy smokers with 35 and 56 years of smoking.

Chronic neuro-endocrine sequelae such as disturbances of growth hormone (GH) and gonadotropin (LH and FSH) regulatory processes are well known among cancer patients and patients with pituitary disease, who received high-dose radiation therapy involving the pituitary-hypothalamic axis (cranial doses > 18 Gy) [19,20,37]. Studies among childhood cancer survivors have demonstrated a higher susceptibility to radiation-induced growth disorders among those treated at the youngest ages [19,21]. However, in agreement with two other studies [23,38], we found no evidence of reduced adult height among subjects treated with NRI in childhood.

Self-reported height in the NRI cohort also showed good agreement with Dutch population-based self-reported data [27], although males younger than 30 years of age in 1997 tended to be slightly less tall than the reference population. However, the subgroup in the NRI cohort consisted mainly of males aged 25-29 years whereas the reference data covered the full range of 20 to 29 year olds. Given the strong and well-described secular trend of increasing height in more recent birth cohorts [39] (clearly demonstrated in our data), the slightly decreased height for this particular age-group in our cohort is likely to be caused by a difference in the age distribution.

Among NRI-exposed females no increased risks were seen for early menarche, early menopause, or subfertility, i.e., reproductive characteristics that can be affected in women who were treated with high-dose cranial radiation, especially at young ages [19,40]. Yeh and others [38] recently reported on prolonged follow-up (> 40 years) of a Maryland cohort of subjects exposed to NRI during childhood. They also found few differences between exposed and non-exposed women with regard to reproductive characteristics, although exposed women were slightly less likely to be still menstruating in 1995, were older at menopause, but, were in general also older than non-exposed women [19]. Our evaluation of menopause is too early for definitive conclusions, as only 12 percent of the women who were first treated before reaching 20 years of age had reached age 50 at end of follow-up. The comparable proportion of postmenopausal women, but higher probability of a surgical menopause among NRI-exposed subjects was surprising. It might be a chance finding, but the issue is of interest to further examine in future follow-up studies of this cohort.

Among males, but not females, treated with NRI a slightly elevated risk of subfertility compared to the non-exposed group (OR=1.4) and a positive dose-response trend was observed. In a study among childhood cancer survivors, male fertility was more affected than female fertility; however, analyses by treatment showed that the difference by sex was restricted to children treated with chemotherapy, and not apparent among patients treated with radiotherapy above the abdomen [41]. Also, no elevated risk of subfertility has been demonstrated in the Maryland cohort [22], at considerably higher pituitary doses compared to our study. Therefore, it is questionable if the observed association with male subfertility represents a true effect. Since half of the cohort is still younger than 40 years, prolonged follow-up, including medical verification, will be useful to address this question in more detail.

The regulation of thyroid stimulating hormone (TSH) levels is usually less sensitive to radiation damage at the hypothalamic-pituitary level compared to both GH and gonadotropin regulation, except for very high dose exposures [37]. Nevertheless, thyroid disorders are of potential interest as the thyroid gland itself was exposed to radiation and is known to be extremely radiosensitive at young ages [42]. Elevated risk of thyroid adenoma after childhood

head and neck radiation has been demonstrated at thyroid doses below 0.2 Gy [42,43]. We did not find a clearly elevated risk for thyroid nodules among NRI-exposed subjects, although more cases were observed among exposed compared to non-exposed females. Of all exposed subjects, only 4 percent received thyroid doses exceeding 4 cGy, and none of these subjects developed thyroid nodular disease. Elevated risks of other thyroid disorders, such as hypothyroidism and Graves' disease, have been reported after high-dose thyroid and/or pituitary radiation exposures among patients receiving cancer treatment (20-60 Gy) [13,14,44]. The lack of association with NRI is not surprising in this respect.

The advantages and limitations of our study design should be taken into account when interpreting our results. The Netherlands NRI cohort is the largest that has been studied to date. Cohort identification was based on individual medical treatment records from participating ENT clinics; therefore, misclassification of exposure status is highly unlikely. The cohort was followed for 18 to over 50 years, with 92 percent of all subjects traced (similar for exposed and non-exposed subjects).

Selection bias is a potential problem as a result of differences between exposed and non-exposed subjects in questionnaire participation. Non-response rates were 13 percent among exposed and 16 percent among non-exposed subjects. However, for the cancer outcomes, a cancer registry linkage procedure (1989-1996) indicated that similar numbers of cancer cases were missed among exposed and non-exposed non-responding subjects [23]. A validation study for the cancer incidence analyses [45] further revealed that failure to obtain consent for medical verification was a major determinant of case ascertainment success rate for both exposed and non-exposed subjects. Although the lack of selective processes with regard to cancer outcomes does not necessarily reflect selection relating to non-cancer outcomes, we would expect any selective effect to be stronger for cancer outcomes. Refusal to participate in the questionnaire survey was also slightly more common among non-exposed (16 percent) than exposed (13 percent) subjects; unfortunately, no data on disease status are available for subjects who refused to participate.

Misclassification of disease outcomes is also a potential problem, as we had to rely on self-report in the questionnaires. However, for benign tumors, non-melanoma skin tumors and thyroid disorders, only medically confirmed diagnoses were included in the analysis. Consent for medical confirmation and availability of medical records limited the medically confirmed cases of thyroid disorders available for analysis to approximately 50 percent of all self-reported cases for both exposed and non-exposed subjects. Among all subjects who reported a history of skin lesions, and were asked for their consent to contact the treating physician, medical verification was permitted by 84 percent of exposed and 77 percent of non-exposed subjects.

We tried to avoid bias by blinding research assistants responsible for coding of disease outcome for exposure status and by not mentioning exposure status in the letters to the treating physicians. We found no evidence of selective physician cooperation, as 85 percent and 90 percent of all requests with regard to verification of thyroid diseases for exposed and non-exposed subjects were returned. For skin tumors, the physician cooperation proportion was over 95 percent in both groups.

Although we did not demonstrate abnormal disease patterns that might result from hormone-regulated processes, we cannot exclude the possibility that low radiation doses to the pituitary gland cause hormone imbalances without clinically overt symptoms. As this study did not involve clinical examinations or blood sampling, no data on hormone levels are available to further evaluate this possibility.

With regard to the analysis we note that some positive findings may be due to chance. We used age-adjusted ORs to estimate underlying risk ratios (RR), although the OR will overestimate the RR if an outcome has a more than 10 percent frequency among non-exposed subjects [46,47]. As this limit is exceeded for all reproductive characteristics the ORs for these variables are likely to slightly overestimate the underlying RR.

In summary, we found no evidence of greatly elevated risk of benign head and neck tumors or thyroid disorders following childhood nasopharyngeal radium irradiation in The Netherlands. Our observation of an increased risk of facial BCC among NRI-exposed subjects is interesting, and this possible association should be explored further in future studies of NRI-exposed populations. There was no clear evidence of radiation-related pituitary gland dysfunction. However, definite conclusions regarding timing of menopause require further prolonged follow-up of our cohort because of the young age of the cohort at present.

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7

General Discussion

This chapter aims to:

- Identify methodological strengths and weaknesses of The Netherlands study on late health effects following NRI,
- Describe various aspects of conducting retrospective cohort studies in The Netherlands, as encountered in the course of the study,
- Put the presented findings into perspective, and
- Identify implications and recommendations for further research.

Methodological considerations

The following sections describe, in chronological order, several methodological issues that we encountered as the study moved forward.

Choice of study design

The Netherlands epidemiologic study into late health effects of NRI was set up as a cohort study. A case-control design is inappropriate for the study of late health effects following NRI, for several reasons. Assessment of NRI-treatment status (yes/no) in a case-control study of brain cancer, for example, is doomed to suffer from serious misclassification bias. Not all patients who were treated with NRI have recollection of the hospital where the treatments were applied, or even of the fact that they were treated by an ear, nose, throat (ENT) physician in early childhood [1].

After reaching adulthood, many subjects will have left the region where they grew up to move to another part of the country. So, even if a case-control study would only include brain cancer cases of one or a few hospitals, the search for original NRI treatment records would involve many different hospitals spread over the country. A fast, automated search is not possible because all medical records covering the decades before 1980 are handwritten. Even if the proper hospital could be traced, then the historical medical record archives covering the decades between 1940 and 1980 would still have to be intact. This is, unfortunately, not always the case (see below for further discussion on this topic).

Another reason for not using a case-control approach is that NRI is a rare exposure in the entire Dutch population. Based on Verduijn's estimate that at least 24,500 treatments have been given in The Netherlands [1], and the total number of inhabitants of The Netherlands

(approximately 16 million), the exposure prevalence is approximately 15 per 10,000 inhabitants. Since a highly elevated relative risk (RR) for brain cancer associated with NRI would not be expected a priori (see also below), a case-control study with sufficient statistical power would require an enormously sized case group. In such a situation, a cohort study tailored to include a sufficient number of exposed subjects, is much more efficient, given the ability to ascertain current disease status (see below).

We applied a retrospective cohort design and identified a well-defined group of patients who were treated with NRI, and a frequency-matched group of other ENT patients, who were never treated with NRI. As pointed out by Shore [2], it would be inappropriate to use any kind of soliciting mechanism to define the cohort since exposed individuals who suffer from a disorder they ascribe to NRI would be more likely to call-in than their healthy NRI-treated counterparts.

The following sections describe three major phases of the cohort study, which are (1) cohort definition, (2) tracing for vital status and current address and (3) ascertainment of disease outcomes. Several related issues will also be discussed.

Cohort definition

Verduijn (1988) [1] initially identified 27 hospitals in The Netherlands where NRI treatments were applied between 1946 and 1981. The estimated total number of treatments per clinic ranged from less than a 100 to over 5,000. The previously defined NRI cohort [1,3], upon which the present study is based in part, was identified in 1982/1983 from five clinics, that were known to have kept treatment records covering the years 1945-1965. Because of financial constraints, only clinics with (relatively speaking) readily accessible medical records were selected for inclusion in the study at that time.

There were several problems with regard to finding intact archives of ENT medical files covering the decades before 1980, the most important of which concerned the way patient medical files were stored. Especially in the early years, it was not uncommon for Dutch specialist physicians to keep their patient administration system themselves, in their office, or even in a private office at home, and some of those systems were never entered into a hospital-wide registration system after the physician retired. Most of such archives cannot be traced anymore. In a few other hospitals the NRI treatment files had been kept, but were known to be small in number, and, more importantly, were spread over medical archives that covered all medical disciplines. Such hospitals were not included in the study since tracing efforts would have been extremely inefficient and costly.

Furthermore, a recent threat to historical medical records is a new privacy law in medicine, adopted in 1995 (WGBO, Wet Geneeskundige Behandelings Overeenkomst) which allows physicians to destroy medical records of patients who have not visited the clinic for more than 10 years. Moreover, after the "introduction" period of the new law has passed (2005), it will even be unlawful to keep old records if there is no clinical necessity to do so, to protect the patient's privacy [4]. The law includes an explicit statement that a physician should keep records if that is felt necessary in terms of "appropriate patient care". However, the definition of "appropriate patient care" has become subject to debate. It may apply to the individual whose record is being kept, but, alternatively, also to the whole population of patients who were treated in a certain way, and whose medical data may hold clues about the etiology of the disease, or late effects of treatments, for example [6-8]. Unfortunately, most legal experts have interpreted the WGBO statement at the individual patient level [4]. In some hospitals, the boards of directors already decided to destroy records of patients that were not seen recently, and for whom there was no medical reason to suspect that the old records would ever be needed again [4,6]. In such decisions not only the patient's privacy, but also financial considerations play a role. Storage of huge piles of old paper records is costly and takes up space that could be used otherwise.

From radiation carcinogenesis we know that the manifestation of excess cancer risk following radiation exposure may take several decades to emerge. Thus, the relevance to our study is that all NRI-treatments took place more than 10 years ago. If the persistent ear, nose, and throat condition was resolved by NRI, the patient (i.e., cohort member) was not seen in the same ENT department over the past 10 years. Moreover, even if head-neck conditions necessitated medical care, mild symptoms may have been treated by family practitioners. In case of severe disorders, only those patients who stayed in the region where they grew up will have consulted an ENT physician of the same department at which the NRI treatment was given. Thus, only individuals, who did not leave their region where they grew up *and* who experienced recurrent, severe ear, nose, throat conditions, will have returned to the same doctor and will have a medical record that was updated less than a decade ago. All others will not have been treated at the same ENT department in the past ten years. Consequently, from a legal standpoint, it would be legitimate to destroy the original medical records that contain essential and unique information for individuals to be included in any study on NRI.

As a result of the above-mentioned problems, the number of NRI-exposed individuals available for the cohort study was limited to approximately one fifth of the total number of NRI-treatments that has been estimated to have been given in The Netherlands [1]. Our medical record search was completed in 1996, i.e., only just after the new law had become effective. It is likely that the full expansion of the cohort, as we conducted in 1995/1996, would no longer be possible at present, because the medical records would have been destroyed in several of the

participating clinics. Colleagues who study late health effects of other types of treatments in The Netherlands, including diethylstilbestrol (DES) and hormonal therapy for infertility (IVF) have had similar experiences [4,6].

Exposure assessment

We were able to estimate radiation doses to tissues of interest for each exposed individual, thanks to the availability of individual treatment records, and information on physical aspects of the radium capsules per clinic. However, an assessment of absorbed doses in tissues very close to the radium capsule is subject to large uncertainties because it is difficult to determine the contribution of β-particles. In addition, the absorbed doses in tissues directly surrounding the nasopharynx are highly dependent on the thickness of the local lymphoid tissue overflow (i.e., the reason for treatment), which is unknown at the individual level. In contrast, known radiosensitive organs (e.g., thyroid gland, salivary glands, brain and breast) are more than 1 cm away from the nasopharynx so that the respective absorbed doses can be estimated with high accuracy as they are the result of exposure to well-understood γ-rays only [7]. Given these uncertainties, the estimation of organ doses in The Netherlands NRI study was done in the best possible way, by an expert radiation physicist, who has a long-standing experience in dosimetric evaluation for studies into late health effects of medical radiation treatments [8-11].

Inclusion of a non-exposed comparison population

We chose to include a non-exposed comparison population, frequency-matched to the exposed individuals by clinic, sex, year of birth, and year of first consultation (both in 5-year categories). The main reason for including such a group, instead of comparing the NRI-exposed subjects to the general population only, is that NRI-exposed subjects might differ from the general population with regard to health-related characteristics. It would be expected that they would differ less from a comparable group of patients who also consulted an ENT physician in childhood. Also, for the general population as comparison group, no data on health-related characteristics are available at the individual level, whereas for the internal comparison group, such characteristics (e.g., smoking behavior, number of diagnostic X-rays, reproductive characteristics) could be ascertained in the same way as for exposed subjects.

Nevertheless, the non-exposed group differs from the exposed group by more than just NRI-treatment status. Very few subjects in our non-exposed group were treated for conditions for which NRI was appropriate, since they were seen in the same clinic as the NRI treated patients. Also, use of the non-exposed group for the analyses severely reduces the number of cases for any given cancer compared to the pool of data from the general population, thereby causing much more variance and statistical uncertainty in the risk estimates [12]. Therefore, we chose to include the non-exposed group but analyze the data both ways. Thus, for study outcomes where population rates were available (cancer incidence and disease-specific mortality) we compared the risk among NRI exposed subjects with both the general population (SMR/SIR analyses) and with the non-exposed group (RR analyses).

Tracing of the cohort for vital status and current address

Individual tracing in The Netherlands is a time-consuming, but rewarding process, owing to the accurate system of municipal population registries, the Central Bureau of Genealogy and the so-called 'Bureau Vestigingsregister' of the Department of Foreign Affairs. We managed to trace 92% of all individuals in the cohort, based on handwritten name and childhood address from the medical chart. Actually, only 3% of the cohort was truly lost to follow-up, as the remaining 5% was known to have emigrated. On average, 1.6 requests per individual were necessary before the whole cohort was traced, with 18% of the cohort requiring 3 or more (up to 12) search requests, corresponding to the number of moves since childhood [13]. The average cost of the whole tracing procedure was ƒ2.71 per individual. Many municipalities charged the standard amount (ƒ1.62) normally applicable to automated searches only [14], although our requests often required timely searches in handwritten person cards. Others charged much more, up to ƒ20,- per request. We are greatly indebted to all municipalities who performed the searches at no charge at all, particularly to the population registry of the city of Sittard, who handled more than a thousand requests at high speed and for free.

At present, all municipal population registries are using a similar computer system (GBA – Gemeentelijke Bevolkings Administratie) and (some) hospitals and research institutes are, or will be permitted, to access the database under strict privacy conditions. As the GBA provides nationwide data, in contrast to municipal-based population registries, future tracing of this and other cohorts will be much less time-consuming, provided GBA-access is granted.

It should be mentioned that the entire tracing process was carried out by research assistants under direct responsibility of the ENT physician in the respective participating hospital.

The municipal population registries are under no circumstance publicly accessible, but allow for use for epidemiologic research. Based on the WGBO, the (current) ENT physician of the hospital where an individual was treated in the past, was responsible for the tracing process and contacting the individual, until he/she had given informed consent for transfer of personal and (explicitly specified) medical data to the NRI study team (see below).

Assessment of disease outcome

Assessment of disease outcome was based on three sources of information, i.e., the nationwide registry of causes of death at Statistics Netherlands, The Netherlands Cancer Registry (NCR), and a questionnaire survey including medical confirmation of self-reported cancers and thyroid disorders.

Our study of cancer mortality based on death certificates (Chapter 2) is valuable because it is not likely to be influenced by selection or information bias and because we traced all but two death certificates. Nevertheless, it has its drawbacks. Although contributing causes of death are available (since the recording of other diseases that were obvious at time of death is mandatory), any potentially lethal, but actually non-fatal disease that occurred earlier in life will not be discovered when using the registry. Moreover, disorders with high survival rates, and disorders that are rarely fatal cannot be studied using cause of death as the main measure of outcome. Furthermore, mortality analyses have to be performed at the office of Statistics Netherlands because individual causes of death cannot be taken outside the institution. Although this procedure did not restrict our ability to analyze the data at present, a future pooled analysis of cancer mortality in all NRI cohorts might be hampered by this policy.

A nationwide cancer registry is an ideal tool for cancer follow-up in a cohort study [15,16]. Unfortunately, the NCR became operational in 1989 only, so that information on cancers that occurred in the cohort between 1950 and 1988 were missed, except for subjects who died of cancer. Another important aspect of incorporating a linkage with the NCR in a study as ours, is the requirement of individual, written consent from all subjects for whom permission can reasonably be obtained, to allow for linkage and reporting of cancer cases at the individual level, not only at present, but also in the future.

Therefore, we contacted all subjects alive as of September 15, 1997 by mail, with a health questionnaire and an informed consent form, the size and wording of which were based on the results of the randomized sub-study described in Chapter 3. The health questionnaire was useful to collect information on cancer (particularly before 1989), non-cancer disorders and life-

style factors (to determine whether NRI-exposed and non-exposed subjects are different in other ways than having been treated with NRI or not). The consent form also was used to allow the investigators to obtain and maintain study files with personal and medical information for this and future studies into the late health effects of NRI. Both the original and the reminder letter stated explicitly that the consent form should be returned blank if the subject chose not to participate in the study. The so-called refusers were not part of the NCR-linkage and were excluded from further study procedures.

There were two subgroups in the cohort, i.e., decedents and true non-responders of the questionnaire survey, for whom linkage with the NCR was eventually allowed without individual consent. The decedents form a group of individuals for whom it was, by definition, impossible to have obtained informed consent for NCR linkage. It should be noted that the latter problem is specific for retrospective cohort studies, as some, and in the most extreme case even all, individuals in such studies will have died before cohort identification takes place. With regard to the non-responders the following regulations applied. The WGBO [17] states that research with medical record data is only allowed if a patient has given informed consent for release of his/her medical files. Nevertheless, conditional upon several requirements with regard to the research protocol, research with coded data from the medical file is in some cases allowed *without* individual consent. Our study design did fulfill WGBO requirements specific to the group of non-responders in that we had applied sufficient tracing efforts and we also had provided at least two, but in most cases many more, occasions to allow for refusal.

According to NCR privacy regulations, additional requirements were set, to protect the privacy of the decedents and the non-responders. Therefore, for these two subgroups of the cohort, we provided the NCR with a computer file that contained study ID, exposure status, and personal (i.e., identifying) information. The NCR assigned a new ID number, and, after the linkage results (i.e., cancer case status) had been added to the computer file, the study ID and the personal data were omitted, before the file was sent back to us. The NCR will keep a key file with original study IDs, new ID numbers, and personal data to allow for linkage in the future.

The linkage with the NCR has produced virtually unbiased estimates of cancer risk in the years 1989-1996, and valuable information on the risk of malignancies in a group of subjects who did not participate in the questionnaire survey (see also below). Future studies of cancer incidence in the NRI cohort will be greatly facilitated by the possibilities of record linkage offered by the NCR. This notion is strengthened by the experience of attempting to trace cancer cases through other mechanisms.

Potential sources of bias introduced by using a questionnaire survey

As the NCR linkage did no cover the whole follow-up period, a questionnaire survey had to fill the gap. We were aware of the fact that the cancers we were most interested in (e.g., thyroid cancer, brain cancer, nasopharynx carcinoma) would not occur frequently in the cohort, because of the size and the young age of the study population. Consequently, any missed cancer would strongly influence the final analyses. Assessment of cancer occurrences before 1989 through a questionnaire survey was felt to be very important.

In each questionnaire survey, high participation rates are of crucial importance to be able to draw valid conclusions upon the findings. Ideally, all subjects who receive a questionnaire complete and return it within a week. In reality, we pre-tested our planned approach procedure (Chapter 3) and, in the final survey, achieved a total participation rate of 71.4%, after two written mailings and a telephone survey. This percentage is in the lower end of a range of participation rates reported for other cohort studies among populations exposed to radiation in childhood (Chapter 3). Although it really is the *participation proportion*100%,* the generally accepted and widely used, but fundamentally incorrect [18], term 'participation rate' is used throughout this thesis.

Roughly a quarter of all cohort members alive as of 1997 did not complete the consent form and the questionnaire, because of either non-response or refusal. The non-response rate was slightly higher among non-exposed subjects. Nevertheless, there was little evidence for differential non-response by exposure or cancer case status: among participants, the overall cancer rates based on NCR linkage (1989-1996) were 10.6 and 9.8 per 10^4 person-years, for exposed and non-exposed subjects, respectively. Corresponding cancer rates for non-responders were 12.6 and 10.7 per 10^4 person-years, respectively. Therefore, we considered non-response not to be a major problem in our study.

However, we cannot exclude the possibility of differential refusal with regard to cancer case status, as we have no further information on individuals who actively chose not to participate in the survey (refusal rates 13% among exposed and 16% among non-exposed subjects). It would have been interesting to know total cancer incidence for exposed and non-exposed refusers, i.e., at the *aggregated* level. Such a record linkage in our study, which is based on medical record information, suffers from too many ethical and privacy problems to be implemented. Nevertheless, if carefully prepared according to the NCR privacy guidelines, in a well-suited epidemiologic study such a linkage could provide useful information on potential biases of using questionnaire data in cancer research, provided that the privacy of the individuals involved is in no way affected.

Medical confirmation of self-reported disorders

Aside from the potential impact of the reasons for non-response or refusal on the value of the study, other potential flaws can be introduced by relying on self-report of disease. Therefore, medical confirmation was sought for neoplastic and thyroid disorders. In general, the Dutch medical system, with its central role for the family practitioner, offers excellent opportunities to trace medical records for a specific illness during the course of life. However, this phase of the study took place in 1998 and was, therefore, in part affected by the problem of destroyed records for the earlier years of the follow-up. Fortunately, pathology reports are usually kept independently of medical records, and are not destroyed as easily. We obtained medical record information in 45% of all self-reported conditions that were author-classified as "probably malignant" or "uncertain" for both exposed and non-exposed subjects (Chapter 4). However, restricted to the 'probably malignant' diagnoses, more than 80% could be verified. Again there was no difference between exposed and non-exposed subjects. For thyroid disorders approximately 50% were medically confirmed (Chapter 6). There were few differences between exposed and non-exposed subjects with regard to the proportion of subjects who gave informed consent for the verification procedure and the proportion of contacted physicians who actually provided medical information.

Ethical considerations

We were aware of the fact that some individuals in the cohort (both NRI-exposed and non-exposed) do not know that an ENT physician treated them in early childhood, or (for exposed subjects) that treatments involved radiation exposure. In addition, we felt that prominently mentioning "radiation" and "cancer" in the letter might have caused more worries and arousal than would be justified based on the a priori hypotheses about the strength of possible associations between NRI and various malignancies. Therefore, we proposed to use a uniform introduction letter for the whole cohort without mention of NRI treatment status, in which the goal of the study would be described in terms of several late health effects (including cancer) after ENT-treatments (including NRI). In all but one participating hospital, the Institutional Review Boards (IRB) approved the proposed letter. In one clinic, however, the IRB insisted that all introductory letters to the respective former patients should include the main study goal, i.e., the tentative association between NRI treatments and development of malignant tumors in later life.

For the whole cohort, we mentioned the telephone number of the study coordinator prominently in the introduction letter, on the questionnaire and on the informed consent form, to allow worried individuals to call us for more information. We thereby made the commitment to reveal full information about the main research questions and, if necessary, to help the individual to trace his or her medical record in the clinic were he/she was treated for ear, nose, throat disorders decades ago. Over 400 calls were registered in the year following the first mailing of the questionnaire survey.

Problems inherent to epidemiologic studies of populations exposed to (very) low radiation doses

Radiation is generally considered to represent a thoroughly studied, and well-understood exposure compared to many other environmental factors. However, this statement should be restricted to radiation at medium to high doses. For doses below 20 cGy it is difficult to study late health effects and to quantify risk within acceptable limits of precision. If one assumes the association of low-LET radiation (i.e., β-particles, γ-rays, and X-rays, see also Chapter 1) and a late health effect, for example brain cancer, to be linear over the whole dose range, than it is possible to project excess risk at high doses to low-dose exposed populations, and calculate the excess number of cases that would be expected to occur after low-dose exposures. For NRI, Shore [2] has published the results of such an exercise, based on the 1994 UNSCEAR report and SEER data on the background rates of site-specific cancers. He demonstrated that among 10,000 NRI-exposed subjects, treated when five years old, the RRs for cancers of the brain, thyroid and salivary gland cancer would be 1.50, 2.53 and 1.45, respectively, and that the corresponding absolute numbers of excess tumors in lifetime would be 55, 36 and 10, respectively.

Such an exercise does not only provide insight into the (potential) impact of this treatment for the health effects of interest, but is also useful to determine the sample size necessary for a valuable study into the late health effects of low dose exposures.

Assuming a 40-year follow-up, Shore [2] demonstrated that a study involving an "infinite unexposed group" would require 4,630 subjects to have the statistical power to demonstrate the excess thyroid cancer risk, but that for brain cancer that number already rose to almost 30,000. Any useful study of salivary gland cancer, a rare tumor, as a late health effect of NRI would require more than 250,000 NRI-exposed subjects.

In 1980, Land [19] illustrated with numerical examples that under-powered studies of late health effects after low-dose radiation exposure, in which testing of multiple disease

outcomes is common, are (1) prone to false-positive results, (2) have a highly elevated probability of false-positive results, which increases with decreasing power (i.e., sample size) and that (3) the amount of bias in the RR estimate also increases with decreasing power. These observations led Shore (1996) [2] to conclude that " (...) thus such a study runs the risk of giving a false reading on both the presence of a risk and the magnitude of that risk. This calls for a very cautious interpretation of findings from low-dose studies".

As NRI treatments in The Netherlands involved lower organ doses compared to those assumed by Shore [2], an even larger cohort would have had to be studied, ideally. We tried to identify all possible individuals who had been treated with NRI in The Netherlands, but, given the estimated total number of treatment in our country of 24,500 [1] it is clear that it would never have been possible to find more than that number of records. Nevertheless, The Netherlands cohort is, by far, the largest of only four existing NRI-cohorts worldwide.

Although the sample size does not meet the prerequisites as calculated by Shore [2], the study was and is important to be conducted for two main reasons. First of all, the uncertainties about radiation effects in the low dose range warrant studies of exposed populations to assess whether there is any important excess of cancer, specific for that type of exposure. In case of NRI, uncertainty about brain tumor risk has concerned many formerly treated subjects. Secondly, several authors have pointed out that the pituitary gland is exposed to higher radiation doses from NRI than is the case with most external X-ray treatments (Chapter 1). Although strong effects on hormonal balances and related disorders have, so far, only been linked to very high dose exposures (>18 Gy at the pituitary gland), it is important to rule out any important non-cancer effects of low to medium radiation doses to this organ (Chapter 6). Of relevance here is the age at exposure, as the majority of children were treated before the age of 10 years, a period in life in which at least some organs are known to be more sensitive to radiation damage than in any other period in life (e.g., thyroid, breast, skin, and pituitary at high doses).

We do recognize that our study cannot prove the null hypothesis of no adverse health effects following NRI. On the other hand, any substantially deviant risk pattern (compared to the non-exposed group or to the general population) would have been detected by now. Therefore, we feel it is important to have conducted this study and to report about it.

Main findings in perspective

Taking all these considerations into account, the following paragraphs present a short overview of the main findings and possible implications, for tissues exposed to medium/high, low, and very low doses of radiation. The definition of these dose-categories is rather arbitrary and based on the distribution of tissue doses in this study

Medium to high-dose exposure (> 1 Gy)

With NRI, tissues in close vicinity of the nasopharyngeal cavity received very high radiation doses (>10 Gy). So far, no elevated cancer risk has been detected (Chapters 2 and 4)[20]. This might be due to cell killing (as postulated by Royal [21]), but another likely explanation is the lack of statistical power to detect an association, as very few cases of pharyngeal carcinoma were expected.

Local lymphoid tissues also received high doses of radiation, but it is unclear if this direct exposure of lymphoid tissue is related to malignancies of the lymphoproliferative system later in life. We demonstrated an approximately two-fold excess risk of NHL in the evaluation of both cancer mortality (SMR=2.6 / RR=3.6) (Chapter 2) and cancer incidence (SIR=2.3 / RR=2.7) (Chapter 4), although both analyses were, in part, based on the same cases. The excess risk could not be linked convincingly to radiation dose in the head and neck area (Chapter 4). In view of the lack of confirmation from the other NRI-cohorts [20,30] and from other radiation studies [23] (see also Chapter 1), and the above-described probability of false-positive results, it is too early to make strong statements on the possible association between NRI and NHL. Existing NRI-cohorts should be followed in the future to see whether the present findings can be strengthened or rejected, based on more substantial numbers of cases.

Low-dose exposure (~ 0.10 – 1 Gy)

No excess of benign pituitary tumors, or of hormone-regulated disorders associated with potential pituitary gland damage were observed, with the exception of the higher probability of reporting a history of subfertility in exposed men (borderline significant), but not women (Chapter 6). Yeh and other (2001) [20] recently demonstrated a decreased risk of cancers in

hormone-sensitive tissues and hypothesized on a role of pituitary radiation damage, although that study did also not find evidence for pituitary gland damage in terms of reproductive characteristics.

In contrast, our risk estimate for breast cancer was slightly, but statistically significantly increased (Chapter 4) (see also below). The possibility that NRI, through pituitary damage, may influence timing of menopause, cannot be addressed appropriately at present, since less than 20% of all women in the cohort had reached menopause as of September 1997. In summary, we find little evidence of pituitary gland damage resulting in clinically important changes in hormone levels and associated disorders (Chapter 6).

Not surprisingly, we did not find an elevated risk of benign salivary gland tumors (Chapter 6) and observed no cases of salivary gland cancer (Chapter 4) in the entire cohort, as our study clearly lacks power to study this disease outcome.

Very low-dose exposure (~ 0.001 – 0.10 Gy)

The brain dose was estimated as the average of doses at 282 anatomical points throughout the brain. Since the brain is a relatively large organ, a wide range of doses (i.e., 0.1 to 37 cGy) is represented, depending on the distance of a particular part of the brain to the nasopharynx (Chapter 2). We did not describe brain cancer risk by specific tumor site and dose because specific information on tumor site was not available for the brain cancers ascertained from death certificates, and also because we did not find evidence of an excess risk of brain cancer overall in association with NRI. The evidence regarding a possible association with NRI is scarce and conflicting (although the highly elevated risk reported by Yeh and others (2001) [20] is not statistically significant). We cannot make definitive statements whether there is elevated risk of brain cancer associated with NRI or not, but, any effect in The Netherlands cohort would likely be less strong compared to the Maryland cohort study, since estimated brain doses were much lower in The Netherlands.

Children who are treated with radiation in the head and neck area, and exposed to 9 cGy or more, are known to be at increased risk of thyroid cancer and benign nodules [24,25]. Four incident thyroid cancers in the exposed group, against 1.4 expected, at an average thyroid dose of 1.5 cGy, represent a potential excess risk in The Netherlands NRI cohort, but the estimate was not statistically significant and confidence intervals were wide(Chapter 4).

With regard to skin cancer elevated risk for BCC of the head-neck area was borderline significant. However, the number of cases among the non-exposed was small, and the

distribution over the body was different from what would have been expected from population data (Chapter 4). The average facial skin dose in The Netherlands NRI study was a factor 10 lower compared to the epidemiologic studies that have demonstrated elevated risk of BCC in radiation-exposed populations [27,28]. Nevertheless, it will be interesting to see whether this risk persists when the cohort is followed over time.

The average dose to the entire active bone marrow (ABM) was extremely low, i.e., below 1 cGy in most subjects, but the average dose to ABM in the head and neck area was higher (1.9 cGy; range, 0.3 – 8.1 cGy). We found no convincing evidence of highly elevated risk of leukemia and multiple myeloma in our study, although both the mortality and the incidence analysis showed positive associations between NRI-exposure and hematopoietic malignancies (Chapters 2 and 4). Although it is known that leukemia can be caused by radiation, evidence linking multiple myeloma to prior radiation exposure is controversial. No excesses for these malignancies have been demonstrated in the Maryland cohort or the submariners cohort [22,30].

Statistically significantly elevated risk for breast cancer was found in the incidence analysis (SIR=1.5) (Chapter 4), and, although not significantly, also in the mortality analysis (SMR=1.7) (Chapter 2). As only one third of all breast cancer cases stems from death certificates, the dependency of these analyses is not as strong as for NHL.

Although the dose to the breast was very low (< 1cGy), the demonstrated slight excess might challenge one to speculate on the role of radiation to the breast itself, but also on the potential role of the dose to the pituitary gland. Yeh and others (2001) [20] based their hypothesis of decreased risk of breast cancer due to pituitary exposure on well-known observations in other studies that the risk of hormone-dependent cancers (e.g., breast, endometrial, ovarian, prostate) is elevated in situations/phases of life that involve elevated hormone-levels in blood. Conversely, they speculated that a decreased level of sex hormones in the blood, indirectly caused by radiation damage to the pituitary gland, may decrease the risk of such cancers [20].

In contrast, Modan and others (1989) [29] reported elevated risk of breast cancer in the Isreali tinea capitis cohort, based on small numbers of cases, and in one subgroup only. The X-ray treatments involved pituitary doses in the order of 44-66 cGy, and breast doses in the order of 1.6 cGy. A recent, preliminary, report on prolonged follow-up showed that the elevated risk had persisted [30], although further details were not provided yet.

As breast cancer risk in our study was most pronounced among individuals who were followed for 30 years or more, we are curious to know whether the so far observed (conflicting) results from the Maryland and The Netherlands NRI cohorts will persist once the cohorts age.

Implications and Recommendations

Comparing the three major cohort studies [20,28] (see also Chapter 1), including ours, it is obvious that results for several cancer sites (brain, breast, NHL) are not uniform. This may be a result of chance, and small population sizes, but it may also point out differences between the NRI-exposed populations, for example with regard to radiation dose. At present, it is not possible to make any definitive statement about these differences.

We also recognize that we studied a heterogeneous group of NRI-exposed subjects. Although we have information on exposure and disease status at the individual level, all our analyses are based on groups of individuals. Therefore, as in many other epidemiologic studies of exposure-disease associations, we cannot exclude the possibility that there are individuals in the cohort, who are extremely sensitive to radiation (e.g., due to their genetic susceptibility) which might have led to tumor induction. We do, however, feel safe to conclude that so far, there is little evidence of highly elevated risks of cancer, benign head and neck tumors or hormonal disorders among subjects who were treated with NRI in The Netherlands. Therefore, we do not see the need for screening programs for NRI-exposed subjects, as have been conducted in the U.S. to detect thyroid cancer in subjects who were exposed to external X-ray treatments as a child (Chapter 1).

If an NRI-exposed subject sees his/her family practitioner or an ENT physician because of worries about late effects of NRI, it is important that a thorough examination of the head-neck area is provided, if only for reassurance of the patient. The Centers for Disease Control and Prevention (CDC) have provided a detailed description of such a procedure [31].

With regard to further research, it is important to prolong follow-up of the three NRI – cohorts, especially since the two childhood cohorts, i.e., the Maryland and The Netherlands cohort, are now entering the ages at which the background risk for cancer is strongly rising. With regard to The Netherlands study, future follow-up will be greatly facilitated by the possibilities for automated record linkage with the population registries (i.e., GBA), the Central Bureau of Geneaology (CBG), the NCR and Statistics Netherlands. Analyses of cause of death and cancer incidence are not useful to address the issue of a possibly increased risk of facial BCC after NRI, and to study timing of menopause. Further study regarding these outcomes will require renewed contact with the participants of the current survey.

To improve the power of the individual cohort studies, a pooled analysis of existing cohorts is recommended.

Furthermore, it would be useful to set up a methodological study to examine cancer risk in subjects who choose not to participate in a given epidemiologic study (as compared to

participants or true non-responders). To be successful in negotiating such an approach with the NCR, it will be necessary to provide privacy protection for those who chose not to participate, in as such that results of the NCR linkage are only requested at the aggregated level. The researchers who perform the study must never have access to the personal identifiers. The latter requirement is, however, not unique to this proposed situation. As aggregated cancer case data are most useful when (at least) broken down by exposure status, sex and age, such a methodological study will have best chances of success in a large-scale epidemiologic study, so that sufficient numbers of cancer cases are available per cell of the aggregated table. The latter is crucial in terms of both useful analysis, and privacy protection.

Finally, it is important to point out that The Netherlands NRI cohort study provides an example of a research question that emerged only after the use of the treatment of interest had been discontinued. If the medical records of a sizable proportion of such patients had not been preserved, the study would not have been feasible. Moreover, had this research question come up today, less than one third of the present cohort could have been included, as all other relevant medical records have been destroyed by now. The availability of original medical treatment records is the first, if not most important, prerequisite for valid studies of long-term adverse treatment effects. Hopefully, joint action by clinicians and epidemiologists will convince the Dutch government that the WGBO privacy law needs adaptation for it has its own adverse side-effects, which are, unfortunately, irreversible once taken place.

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Summary

This thesis describes a follow-up study of Dutch patients who were treated with nasopharyngeal radium irradiation (NRI) for Eustachian tube dysfunction, in the decades after WW-II.

Historically, radium and X-rays were applied for many medical and industrial purposes (Chapter 1). Although risks of chronic exposure to high doses of radiation have been described early on, recognition of potential long-term effect took, by definition, much longer to evolve. NRI was abolished gradually between 1960 and 1980, as reports appeared on radiation-induced thyroid cancer among children treated with external X-rays for benign head and neck disorders. So far, epidemiologic evidence on possible late health effects of NRI is scarce, and no strongly elevated risk for any health outcome has been demonstrated. Nevertheless, a 1982 report on a follow-up study of a Maryland NRI-cohort revealed a suggestive elevated risk of brain cancer and a slightly decreased risk of breast cancer. The authors speculated on the possible role of radiation-related damage to the pituitary gland. Although the risk estimates were not statistically significant, these results have given rise to public concern and scientific controversy over the possible late health effects following NRI treatment in childhood. A 1995 workshop on "the public health response to nasopharyngeal radium irradiation" resulted in recommendations for additional research. Accordingly, follow-up of the Netherlands NRI cohort study, initiated in 1982 by Dr PG Verduijn, was prolonged and the size of the cohort was doubled (Chapter 1).

We conducted a retrospective cohort study of 5,358 NRI-exposed and 5,265 frequency-matched non-exposed subjects in The Netherlands (Chapter 2). The cohort was defined based on original patient records in nine participating ENT clinics. The average radiation doses were 275, 11, 1.8, and 1.5 cGy for nasopharynx, pituitary, brain, and thyroid, respectively. The cohort included 57 percent males. Fifty-two percent of NRI-exposed subjects had their first radiation treatment between the ages of 5 and 9 years, 21 percent were treated before the age of 5 years, and 11 percent were treated after the age of 19 years. Ninety-two percent of the entire cohort was traced through a search at population registries with a median follow-up of 31.6 years. The median attained age of those alive in 1997 was 41 years (range, 18-87 years).

We first studied overall, and cancer-specific mortality following NRI based on the entire cohort (Chapter 2). For all but two decedents, death certificates were obtained at Statistics Netherlands. Three hundred and two NRI-exposed subjects had died (SMR = 1.1, 95% confidence interval [CI]: 1.0 to 1.3), which was similar to the mortality among non-exposed subjects (SMR = 1.1, 95% CI: 0.99 to 1.2). We found no excess deaths from cancers in the head and neck area among exposed subjects (SMR = 0.9, 95% CI: 0.3 to 2.2). However, there were

excess deaths from cancers of lymphoproliferative and hematopoietic origin (SMR = 1.9, 95% CI: 1.1 to 3.0), mainly from non-Hodgkin's lymphoma (NHL) (SMR = 2.6, 95% CI: 1.0 to 5.3). Excess risk of NHL has not been demonstrated in other radiation-exposed populations, including three other NRI-cohorts. Despite speculation by other researchers on NRI-associated, radiation-induced pituitary gland damage and subsequent decreased risk of hormone-dependent cancers, we found slightly more breast cancer deaths than expected (SMR = 1.7, 95% CI: 0.9 to 2.8). In interpreting these results, it is important to take the possibility of chance findings into account, as the number of cases per cancer site was small. In conclusion, this study does not indicate strongly increased cancer mortality risk in a population exposed to NRI in childhood.

All other analyses of the Netherlands NRI cohort were, at least in part, based on data derived from a health questionnaire survey among all subjects alive as of September 15, 1997. We first conducted a randomized study among 200 subjects, to test the influence on participation rates of two differently sized questionnaires and two types of informed consent forms, i.e., a basic form and a multiple-option form (Chapter 3). Although not statistically significantly so, the participation rate was 10 percent lower in the subgroup that received the long questionnaire, compared to the short-questionnaire subgroup. There was no difference in participation rate with regard to type of consent form, and, few subjects actually used the possibility to give partial consent on the multi-option form. Based on these results, we decided to use a short questionnaire and a basic consent form in the final NRI questionnaire survey

The second part of Chapter 3 describes results of the final NRI questionnaire survey by approach strategy and population characteristics. The survey consisted of two mailings and a telephone survey among non-responders. Since four smaller participating clinics were not involved in the telephone survey, the presented analyses included 8,402 out of 9,142 subjects known to be alive as of September 1997. The total participation rate in the eligible cohort was 74 percent, of which the last 10 percent were achieved through the telephone survey. Exposed subjects, females, subjects younger than 70 years at questionnaire completion, and subjects who had been included in the 1985 questionnaire survey of this cohort were more likely to participate than non-exposed subjects, males, subjects older than 70 years of age at questionnaire completion and subjects in the "new" part of the cohort, respectively. Non-participating males were more likely to not respond rather than refuse, whereas a trend of increasing refusal rates, but not non-response rates, with advancing age at questionnaire completion was demonstrated.
We then studied cancer incidence among 4,339 NRI-exposed and 4,104 non-exposed subjects (Chapter 4) based on cancer registry linkage (1989-1996), self-report including medical verification (1945-1988) and death certificates (1945-1996). During an 18-50 year follow-up, fourteen malignancies of the head and neck occurred among exposed subjects, which was close to the expected number of cases (SIR 1.2, 95% CI: 0.6 to 2.8). These included four thyroid

malignancies (SIR 2.8, 95% CI: 0.8 to 7.2) and five malignant brain tumors (SIR 1.3, 95% CI: 0.4 to 3.1). Increased risks were observed for malignancies of lymphoproliferative and hematopoietic origin (SIR 1.9, 95% CI: 1.2 to 2.8) and breast cancer (SIR 1.5, 95% CI: 1.1 to 2.1). In the non-exposed group, SIRs for most cancer sites were close to unity. Strong dose-response trends could not be demonstrated for any cancer outcome although RRs were elevated in the highest dose category for head-and-neck cancer and breast cancer. Risk estimates for breast cancer were based on extremely small breast doses (< 0.1 cGy), and an opposite relationship (i.e., decreased risk of hormone-related cancers) was demonstrated in another NRI cohort. These data provide little evidence for a high excess risk of cancer associated with NRI treatment. Inconsistent findings across studies and public concern warrant further prolonged follow-up of available cohorts.

Based on the cancer incidence study described in Chapter 4, we conducted a validation study to assess the accuracy of self-reported cancer occurrences, with and without medical verification, against cancer registry linkage (Chapter 5). This study is based on all 6,528 participants (mean age 41 years) of the health questionnaire survey. Four questionnaire items, on tumors/growths, hospital admissions, biopsies, and radiotherapy, were used as clues to identify possible cases. Self-reported diagnoses were author-classified as probably benign, probably malignant, or uncertain with regard to type of disorder. After written consent, medical verification was sought for diagnoses classified as probably malignant or uncertain.

Linkage with the Netherlands Cancer Registry revealed 55 invasive tumors (1989-1996). The positive predictive value (PPV) of self-report itself, without investigator interpretation, was poor. However, for self-reported diagnoses that had been author-classified as probably malignant (N=65), sensitivity was 0.78 and the PPV was 0.66. The PPV rose to 0.91 for medically verified cases (N=43). Of twelve false-negative cases, a total of seven were due to failure to obtain consent for medical verification. Women reported better than men, but we found no difference by exposure status. The questionnaire survey revealed another four cancers that were not reported in the cancer registry linkage.

The study shows that self-reported diagnoses, in combination with investigator-interpretation and medical verification, results in a high PPV and a reasonably high sensitivity for most tumors in a not particularly health-conscious population.

Finally, Chapter 6 evaluates non-cancer disorders (i.e., thyroid disorders and conditions related to regulatory control of anterior pituitary hormones) and non-melanoma skin cancers (NMSC) in the Netherlands NRI cohort. This study included all participants of the questionnaire survey, 3,440 NRI-exposed and 3,088 non-exposed subjects. Disease status (including medical confirmation) and indicators of pituitary gland radiation damage (height and reproductive characteristics) were assessed from the 1997 questionnaire survey. In addition, we tried to

medically verify all NMSC, benign tumors and thyroid disorders. Among exposed subjects, 23 benign head-neck tumors were observed, compared to 21 among non-exposed subjects. Elevated risk of basal cell carcinoma (BCC) of the head and neck area was observed in exposed subjects (OR = 2.6, 95% confidence interval (CI): 1.0 to 6.7). However, the risk estimate is likely to be biased since the non-exposed group showed a deviant pattern with regard to the distribution of BCC over the body (as compared to population data). It will be interesting to follow this population in the future to check whether the risk remains elevated.
Exposed and non-exposed groups did not differ substantially with regard to thyroid disorders, height and reproductive characteristics, although exposed males more frequently reported a history of subfertility compared to non-exposed males (OR=1.4, 95% CI: 1.0-2.1). Among males but not among females there was evidence of a trend in risk with increasing radiation dose to the pituitary gland. It is questionable if the observed association with male subfertility represents a true effect.

We found no strong evidence of a highly elevated risk of benign head and neck tumors, NMSC, thyroid disorders or indicators of pituitary radiation damage, 18-50 years following childhood nasopharyngeal radium irradiation in the Netherlands.

In Chapter 7 several methodological issues encountered during the conduct of the study are described, most importantly, the problems in cohort definition due to destroyed, or inaccessible medical files, the possibility of cancer registry linkage for non-responders and decedents (without individual consent, but under a more strict privacy protection protocol), and general problems in the interpretation of results from studies on (very) low dose radiation exposures. Based on the studies presented in this thesis, recommendations for future research include further prolonged follow-up of the existing NRI-cohorts, and a pooled analysis of all NRI-cohorts. A third recommendation includes a methodological study of cancer incidence among individuals who choose not to participate in a particular questionnaire survey, and do not allow cancer registry linkage.

Finally, attention is drawn to a new Dutch privacy law in medicine (WGBO), which allows for large-scale destruction of historical medical records, particularly after 2005. Hope is expressed that the WGBO can be adapted in such a way that medical records crucial for the evaluation of late treatment effects will no longer be threatened by the possibility of being destroyed.

Samenvatting

In dit proefschrift wordt een epidemiologisch onderzoek beschreven onder patiënten die in het verleden door hun keel-, neus- en oorarts (KNO) zijn behandeld met radium, ofwel, met nasofarygeale radium bestraling. Deze behandeling werd tussen 1945 en 1970 voornamelijk toegepast bij kinderen met chronische oorontstekingen.

Radium en röntgenstralen worden sinds het begin van de 20e eeuw gebruikt voor medische behandelingen (Hoofdstuk 1). Al binnen enkele jaren na de ontdekking van radium was het bekend dat langdurige blootstelling aan straling negatieve bijwerkingen op de gezondheid kan hebben. Echter, het heeft tientallen jaren geduurd voordat ook de lange-termijn effecten in kaart gebracht konden worden. Nasofaryngeale radium bestraling is tussen 1960 en 1980 geleidelijk verdwenen uit de dagelijkse praktijk van de KNO-arts. Eén van de aanleidingen daarvoor was het groeiende bewijs dat patiënten die als kind met röntgenstralen waren behandeld voor goedaardige aandoeningen in het hoofd-hals gebied, op (jong)-volwassen leeftijd een verhoogde kans op schildklierkanker hebben.

Tot op heden zijn er wereldwijd slechts vier epidemiologische studies gedaan naar de mogelijke late gezondheidseffecten van nasofaryngeale radiumbestraling. De beschikbare onderzoeksresultaten hebben geen sterk verhoogd risico op kanker aangetoond, hoewel een Amerikaans onderzoeksteam in 1982 wel een mogelijk verhoogd risico op hersentumoren, en een *verlaagde* kans op hormoon-gerelateerde tumoren rapporteerde. Zij speculeerden daarbij over een mogelijke rol van de hypofyse, die door de ligging in de buurt van de nasofarynx, relatief hoge doses straling heeft ontvangen bij de radiumbehandeling.

In 1995 is er in de Verenigde Staten een workshop georganiseerd, met als titel 'the public health response to nasoparyngeal radium irradiation' waarbij experts uit alle relevante disciplines bijeengekomen zijn en (onder andere) aanbevelingen hebben gedaan voor verder onderzoek. Mede naar aanleiding van deze workshop, hebben wij een oorspronkelijk in 1982 door Dr PG Verduijn gedefineerd radium cohort in omvang verdubbeld, en vervolgens gevolgd tot in 1997 (Hoofdstuk 1).

Het retrospectieve cohort onderzoek omvatte 5358 bestraalde patiënten en 5265 KNO-patiënten die niet met radium waren behandeld (de "vergelijkingsgroep"), gematcht op algemene populatie kenmerken en kliniek. Het cohort werd geïdentificeerd op basis van medische dossiers in negen deelnemende ziekenhuizen. De gemiddelde doses straling voor nasofarynx, hypofyse, hersenen en schildklier waren respectievelijk 275, 11, 1.8, en 1.5 cGy. Het cohort bestond voor

57 procent uit mannen. Iets meer dan de helft van de bestraalde patiënten was tussen de 5 en 9 jaar bij behandeling, terwijl nog eens 21 procent jonger was dan 5 jaar. Slechts een tiende van alle bestraalde patiënten in dit onderzoek is op volwassen leeftijd behandeld. Na een intensieve zoektocht bij gemeentelijke bevolkingsregisters hebben we 92 procent van alle patiënten in het cohort opgespoord; De mediane follow-up was 31.6 jaar en de leeftijd in 1997 varieerde van 18 tot 87, met een mediaan van 41 jaar.

Allereerst hebben we de sterfte ten gevolge van kanker bestudeerd (Hoofdstuk 2). Voor alle overledenen, op twee na, hebben we de doodsoorzaak weten te achterhalen bij het Centraal Bureau voor de Statistiek. In de met radium behandelde groep waren tot 1997 in totaal 302 personen overleden (Standardized Mortality Ratio (SMR) = 1.1, 95% betrouwbaarheidsinterval (BI): 1.0-1.3), hetgeen overeenkwam met de total sterfte in de vergelijkingsgroep (SMR = 1.1, 95% BI: 0.99-1.2). We vonden geen bewijs voor een verhoogde sterfte ten gevolge van hoofd-hals tumoren (SMR = 0.9, 95% BI: 0.3-2.2). Er bleek wel verhoogde sterfte ten gevolge van maligniteiten van bloedvormende weefsels en lymfestelsel (SMR = 1.9, 95% BI: 1.1-3.0), dat voornamelijk tot uitdrukking kwam in een verhoogd risico op sterfte door een non-Hodgkin's lymphoma (NHL) (SMR = 2.6, 95% BI: 1.0-5.3). Andere onderzoeken naar de late gezondheidseffecten van straling, inclusief de nasofaryngeale radiumbehandeling, tonen doorgaans geen verband tussen straling en NHL. In tegenstelling tot de speculatie van Amerikaanse onderzoekers over een *verlaagde* kans op hormoon-gerelateerde kankers na radiumbehandeling, vonden wij een licht verhoogde sterfte ten gevolge van borstkanker (SMR = 1.7, 95% BI: 0.9 tot 2.8). Bij de interpretatie van voorgenoemde resultaten is het belangrijk de mogelijkheid van toevalsbevindingen te onderkennen omdat het aantal sterfgevallen per type kanker klein was. Deze onderzoeksresultaten wijzen niet op een sterk verhoogde kankersterfte onder personen die als kind met radium zijn behandeld.

De overige analyses binnen de Nederlandse Radium Cohort Studie zijn (deels) gebaseerd op gegevens uit een vragenlijstonderzoek dat we hebben uitgevoerd onder alle personen die in september 1997 in leven waren. Eerst hebben we een gerandomiseerde studie uitgevoerd onder 200 personen in het cohort, zodat we de invloed van vragenlijstomvang en type toestemmingsverklaring op de respons konden testen (Hoofdstuk 3). Daaruit bleek dat het deelnemerspercentage (statistisch niet-significant) 10 procent hoger was bij gebruik van een korte vragenlijst, in vergelijking met een lange vragenlijst. Daarentegen vonden we vergelijkbare deelnemerspercentages bij gebruik van een standaard toestemmingsverklaring of een toestemmingsverklaring die per studie-onderdeel de mogelijkheid voor deelname dan wel weigering bood. Omdat maar zeer weinig deelnemers gedeeltelijke toestemming voor het onderzoek gaven, hebben we in het uiteindelijke vragenlijstonderzoek gebruik gemaakt van een standaard deelnemersverklaring en een korte vragenlijst.

De tweede helft van Hoofdstuk 3 beschrijft deelname, weigering en non-respons (=geen reaktie) in het uiteindelijke vragenlijstonderzoek per fase van het onderzoek, en uitgesplitst naar verschillende populatiekenmerken. Het vragenlijstonderzoek bestond uit twee schriftelijke benaderingen en een telefonische enquête onder non-responders. De gepresenteerde resultaten hebben betrekking op 8402 personen die in het verleden waren behandeld in een van de vijf grotere deelnemende ziekenhuizen. De totale deelname was 74 procent, waarvan de laatste 10 procent resulteerde uit de telefonische enquête. Uitgesplitst naar populatiekenmerken was het deelnamepercentage hoger voor de radiumgroep v.s. de vergelijkingsgroep, voor vrouwen vergeleken met mannen, voor personen <70 dan voor oudere personen en voor personen die in 1985 al eens waren benaderd voor een vragenlijstonderzoek vergeleken met personen die voor het eerst werden aangeschreven in 1997. Niet-deelnemende mannen bleken vaker non-responders dan weigeraars te zijn, terwijl het omgekeerde gold voor niet-deelnemers ouder dan 60 jaar.

Vervolgens hebben we de incidentie van kanker bestudeerd bij 4339 met radium behandelde personen en 4104 personen uit de vergelijkingsgroep (Hoofdstuk 4). Het vóórkomen van kanker is bepaald aan de hand van een koppeling met de Nederlandse Kanker Registratie (1989-1996), zelfrapportage gevolgd door medische verificatie (1945-1988) en doodsoorzaak (1945-1996). De follow-up periode varieerde van 18 tot 50 jaar, en daarbinnen vonden we, in overeenstemming met het verwachting, 14 gevallen van kwaadaardige hoofd-hals tumoren (Standardized Incidence Ratio (SIR) 1.2, 95% BI: 0.6-2.8). Daaronder waren vier gevallen van schildklierkanker (SIR 2.8, 95% BI: 0.8-7.2) en vijf kwaadaardige hersentumoren (SIR 1.3, 95% BI: 0.4-3.1). We vonden verhoogde risico's voor maligniteiten van bloedvormende weefsels en lymfestelsel (SIR 1.9, 95% BI: 1.2-2.8) en borstkanker (SIR 1.5, 95% BI: 1.1-2.1). In de vergelijkingsgroep daarentegen waren de SIRs voor de meeste typen kanker niet ver van 1. We konden geen sterke dosis-effect relaties aantonen, hoewel de relatieve risico's (RR) voor borstkanker en hoofd-hals tumoren verhoogd waren in de subgroep die was blootgesteld aan de hoogste doses. Bij een radiumbehandeling is de dosis straling die de borst kan bereiken nog maar zeer laag (< 0.1 cGy). Bovendien hebben andere onderzoekers een verlaagd risico voor hormoon-gerelateerde kankers aangetoond. Wij concluderen dat deze resultaten geen duidelijke aanwijzingen bevatten voor een sterk verhoogd risico op kanker na behandeling met nasofaryngeale radiumbestraling. Inconsistenties in de bevindingen van verschillende onderzoeken en publieke ongerustheid vormen voldoende aanleiding om alle radiumcohorten in de toekomst te blijven volgen.

Als onderdeel van het hierboven beschreven onderzoek naar de incidentie van kanker (Hoofdstuk 4) is nagegaan hoe accuraat de incidentie van kanker ingeschat kan worden op basis van zelf-rapportage, al dan niet aangevuld met medische verificatie, in vergelijking met de

gegevens van de Nederlandse Kanker Registratie (Hoofdstuk 5). Dit onderzoek is gebaseerd op alle 6528 deelnemers van het vragenlijstonderzoek. We hebben vier vragen uit de lijst gebruikt om mogelijke tumoren te identificeren, namelijk, vragen over tumoren en bobbeltjes, ziekenhuisopnamen, weefselonderzoek en bestralingen. Vervolgens werden de zelf-gerapporteerde aandoeningen door een van de onderzoekers geclassificeerd als waarschijnlijk-goedaardig, waarschijnlijk-kwaadaardig, of niet-classificeerbaar. Alleen bij toestemming van de betrokken deelnemer, hebben we vervolgens getracht de waarschijnlijk kwaadaardige en niet-classificeerbare aandoeningen te verifiëren bij de behandelend huisarts of specialist.

Volgens de koppeling met de Nederlandse Kanker Registratie waren in de periode 1989-1996 in totaal 55 invasieve tumoren opgetreden. De positief-voorspellende waarde (PPV) van alleen zelf-rapportage was erg laag. Voor de 65 zelf-gerapporteerde tumoren die als waarschijnlijk-kwaadaardig waren geclassificeerd, waren sensitiviteit 0.78 en PPV 0.66. Bij restrictie tot medisch-geverifieerde tumoren (N=43) steeg de PPV tot 0.91. Zeven van de twaalf vals-negatieve gevallen van kanker konden niet geverifieerd worden vanwege een gebrek aan toestemming van de betreffende deelnemer. Vrouwen bleken kanker beter te rapporteren dan mannen, maar we vonden geen verschil tussen de met radium behandelde groep en de vergelijkingsgroep. Verder zijn uit de zelfrapportage gevolgd door medische verificatie vier kankergevallen naar voren gekomen, die niet uit de koppeling met de kankerregistratie waren gebleken. Dit onderzoek toont aan dat zelf-rapportage, na interpretatie door de onderzoeker en gevolgd door medische verificatie, een hoge PPV oplevert en een acceptabele sensitiviteit in een onderzoekspopulatie die geen bijzondere belangstelling voor gezondheidsvraagstukken heeft.

Hoofdstuk 6 beschrijft het vóórkomen van niet-kanker aandoeningen, zoals schildklierziekten, en aandoeningen die in verband staan met hormoonregulatie door de hypofyse (groei, vruchtbaarheid) en van niet-melanoom huid kankers (NMSC) in het Nederlandse radium cohort onderzoek. Dit onderdeel van het onderzoek heeft betrekking op deelnemers van het vragenlijstonderzoek, te weten 3440 met radium behandelde personen en 3088 personen uit de vergelijkingsgroep. Het vóórkomen van dergelijke aandoeningen werd bepaald aan de hand van de vragenlijsten, en we hebben getracht alle NMSC, benigne tumoren en schildklierziekten medisch te verifieren. In de radiumgroep vonden we 23 goedaardige tumoren van het hoofd-hals gebied in vergelijking tot 21 in de vergelijkingsgroep. Er bleek een verhoogd risico te zijn op basaal cel carcinomen (BCC) van de huid in het hoofd-hals gebied (Odds Ratio (OR) = 2.6, 95% BI: 1.0-6.7). Aangezien de vergelijkingsgroep een afwijkend patroon vertoonde voor wat betreft verdeling van BCC over het lichaam (in vergelijking tot de algemene bevolking) is de OR van 2.6 waarschijnlijk vertekend en moeilijk te interpreteren. Het zal interessant zijn dit cohort in de toekomst te volgen om na te gaan of het ogenschijnlijk verhoogde risico op BCC gehandhaaft blijft, of een artefact blijkt te zijn. De radium- en vergelijkingsgroep verschilden nauwelijks van

elkaar wat betreft het vóórkomen van schildklieraandoeningen en reproductieve factoren en lichaamslengte. In tegenstelling tot de vrouwen, bleken met radium behandelde mannen iets vaker vruchtbaarheidsproblemen te rapporteren dan de mannen in de vergelijkingsgroep. Het risico was verhoogd onder mannen die aan de hoogste doses waren blootgesteld. Het is mogelijk dat dit een toevalsbevinding is.

Samenvattend, leveren deze resultaten geen aanwijzingen voor sterk verhoogde risico's op goedaardige hoofd-hals tumoren, NMSC, schildklieraandoeningen of gevolgen van hypofyse beschadiging onder personen die tientallen jaren eerder met radium waren behandeld in Nederland.

In Hoofdstuk 7 worden verschillende methodologische aspecten van dit cohort onderzoek beschreven. De belangrijkste onderwerpen betreffen de moeilijkheden bij het definiëren van het cohort vanwege de beperkte beschikbaarheid van (toegankelijke) medische dossiers en de mogelijkheid om overledenen en non-responders zonder individuele toestemming, maar met meer privacy-beschermende maatregelen, te koppelen met de Nederlandse Kanker Registratie. Daarnaast worden algemene problemen besproken bij de interpretatie van resultaten uit zogenaamde 'lage-dosis' studies.

De studies die zijn gepresenteerd in dit proefschrift hebben geleid tot de volgende drie aanbevelingen voor verder onderzoek: (1) het in de toekomst blijven volgen van met radium behandelde cohorten (2) een gepoolde analyse van de beschikbare cohorten, en (3) een methodologisch onderzoek naar de incidentie van kanker onder personen die ervoor kiezen niet deel te nemen aan wetenschappelijk onderzoek waarvoor ze zijn uitgenodigd, en die dus geen toestemming geven voor individuele koppeling met de kankerregistratie. Tenslotte wordt de privacy wetgeving in het Nederlandse gezondheidszorgsysteem, in het bijzonder de WGBO, onder de aandacht gebracht, omdat onder deze wet historische medische archieven bedreigd worden met vernietiging. Het zou wenselijk zijn indien de WGBO dusdanig aangepast kan worden dat medische gegevens die cruciaal zijn voor onderzoek naar late effecten bewaard blijven.

Appendix

Radium applicator and unilateral treatment characteristics by clinic in the Netherlands NRI study

Clinic	No. of patients	Source activity (mg)	No. of Sessions	Interval	Session duration*	Treatment prescription dose†		
						Mean	Minimum	Maximum
1	3,401	24.77	4	1 week	age <17 yrs: 7 min age 17+ yrs: 15 min	12.8	2.9	74.3
2	567	50	3	2-4 weeks	20 min	43.6	13.3	66.7
3	736	25	4	1 week	20 min	24.7	8.3	66.7
4	140	10	1-3	up to 1 year	60 min	15.8	10.0	30.0
5	136	25	3	1-2 weeks	children: 4, 9, 13 min adults: 9, 17, 26 min	13.7	5.4	25.4
6	237	50.03	2-3	2 weeks	range 6-24 min ; correlates with age	24.5	3.3	60.0
7	87	25	1-3	4 weeks (up to 1 year)	7-10 min	6.7	2.9	11.3
8	54	31.47	3	1 week	2, 3, 5 min	7.7	2.6	32.6
Total	5,358					18.2	2.6	74.3

* treatment times refer to unilateral treatments for all clinics except for clinic 2, where bilateral treatment sessions were standard, i.e., 10 minutes left nostril and subsequently 10 minutes right nostril in one session;

† treatment prescription dose defined as the product of the radium source activity (mg) and the total duration of the radium treatments (hours)

List of Publications

Ronckers CM, Land CE, Verduijn PG, Hayes RB, Stovall M, van Leeuwen FE. Cancer mortality after nasopharyngeal radium irradiation in The Netherlands: a cohort study. J Natl Cancer Inst 2001;93:1021-7 (by permission of Oxford University Press).

Ronckers CM, Land CE, Hayes RB, Verduijn PG, van Leeuwen FE. Response-behavior in a mailed health questionnaire survey as part of a retrospective cohort study (submitted for publication).

Ronckers CM, van Leeuwen FE, Hayes RB, Verduijn PG, Stovall M, Land CE. Long-term cancer incidence following nasopharyngeal radium irradiation (submitted for publication).

Ronckers CM, Schouten LJ, Land CE, Verduijn PG, van Leeuwen FE. Assessment of cancer incidence from health questionnaire data: a validation study (submitted for publication).

Ronckers CM, Land CE, Hayes RB, Verduijn PG, Stovall M, van Leeuwen FE. Late health effects of childhood nasopharyngeal radium irradiation: non-melanoma skin cancers, benign tumors and hormonal disorders (submitted for publication).

Dankwoord

Sinds mijn eerste werkdag in de Reinaert Kliniek, zijn 6 jaar en 3 weken vergaan. In die tijd hebben velen een steentje bijgedragen aan het project "proefschrift Cécile". Ik wil graag bedanken, met diep respect, Floor van Leeuwen voor stimulans, stok-achter-de-deur, vertrouwen en vriendschap, en Pim Verduijn voor onverzettelijkheid, optimisme en openhartige gesprekken op weg van en naar Amsterdam. Ik dank alle oud-KNO-patiënten die aan dit onderzoek hebben deelgenomen. Ik dank mijn collega's van de Reinaert Kliniek, in het bijzonder Marij & José die er al die tijd bij waren, voor honderden kopjes koffie en gezelligheid, en de hardwerkende en vrolijke onderzoeksassistenten Monique de Kok, Monique Mommers, Marion Kappert, Suzanne Schefman, Rob Wilting en Ton Frank Bekkers. Een bijzonder woord van dank aan de deelnemende KNO-artsen en hun personeel, in het bijzonder Mariet, Nel, Lizzy en Conny van de poli KNO in Sittard, voor de hartelijke ontvangst & welkome hulp bij het archiefonderzoek, en aan de leden van het gezin Verduijn, die allen een steentje hebben bijgedragen aan dit project. Ik dank Neil Aaronson voor gastvrijheid om te werken bij PSOE in Amsterdam, alle collega's van PSOE, en in het bijzonder Helen Klip, Janneke Verloop, en Evelien de Boer voor vriendschap en hulp-waar-nodig, en Matti Rookus, Marja van den Hoorn, Marian Chin-a-Kwie en Willem Klokman voor tijd en aandacht bij vragen en probleempjes. Ik dank Leo Schouten voor de prettige en efficiënte samenwerking en Piet van den Brandt wiens vakkennis en enthousiasme mijn interesse voor de (kanker) epidemiologie hebben gewekt. A very special "thank you" to Charles Land and Elaine Ron who invited me to come to the DC-area and work at NCI's Radiation Epidemiology Branch from November 1999 through May 2000, a period of time which affected many aspects of my life. With respect, I thank Richard Hayes, Marilyn Stovall and Charles Land for being gentle and patient and yet attentive and critical towards my work. I am greatly indepted to Diane Fuchs, who guided us through administative hassles in the earlier days of the project, and who became a dear friend in the past two years. Ik dank mijn vrienden en familieleden voor hun belangstelling en kameraadschap; zonder iemand te kort te willen doen, noem ik in het bijzonder Annemarie Ronckers, Sandra de Waal-Valkenburg, Jacqueline Peeters-Jacobs en mijn beide "parapimfen" Chantal Ruijten en Monique Mommers. Ik dank De Enige Echte Epi-Ladies, Agnes Schuurman, Peggy van den Hoogen, Helen Klip, Anita Botterweck, Loes van Herten en Monique de Kok voor vriendschap, luisterend epi-deskundig oor, en gezellige uitstapjes. Ich danke mein Micha für Liebe, Humor und Unterstützung im letzten Teil dieser Arbeit, en ik dank mijn vaste bakens, pap en mam, voor nimmer-aflatende steun, en vertrouwen in deze ietwat impulsieve dochter.

Curriculum vitae

Cécile Ronckers werd geboren op 11 maart 1971 in Linne. In 1989 behaalde zij het atheneum diploma aan de Rijksscholengemeenschap te Roermond waarna zij begon aan de studie Gezondheidswetenschappen aan de Rijksuniversiteit Limburg (de huidige Universiteit Maastricht). Na het afsluiten van doctoraalfase Biologische Gezondheidkunde, en een stage bij de Vakgroep Humane Biologie van de Rijksuniversiteit Limburg in 1993, heeft zij het keuze-tracé Methoden en Technieken van Epidemiologisch Onderzoek gevolgd en vervolgens twee verdere onderzoeksstages voltooid, bij de Nederlandse Cohort Studie naar Voeding en Kanker aan de Capaciteitsgroep Epidemiologie van de Rijksuniversiteit Limburg, en op het gebied van de Fertiliteitsgeneeskunde, een samenwerkingsproject van de Divisie Obstetrie en Gynaecologie van het Academisch Ziekenhuis Utrecht en het instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam. Sedert het afstuderen en de registratie als Epidemioloog A in 1995, is zij werkzaam geweest als dagelijks coördinator van het landelijk cohort onderzoek naar de late gezondheidseffecten van nasofaryngeale radiumbestraling. Het grootste deel van het onderzoek is uitgevoerd in de Reinaert Kliniek te Maastricht. Tijdens deze periode werkte zij regelmatig een dag als gast bij de Afdeling Epidemiologie van het Nederlands Kanker Instituut te Amsterdam. Van november 1999 tot in mei 2000 zijn de werkzaamheden voor dit project verlegd naar de Radiation Epidemiology Branch, binnen de Division of Cancer Epidemiology and Genetics van het Amerikaanse National Cancer Institute (Rockville, Maryland). Op 1 december 2001 zal zij bij deze afdeling als Visiting Post-Doctoral Fellow in dienst treden.