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# Estimating the risk for secondary cancer following targeted alpha therapy with astatine-211 intraperitoneal radioimmunotherapy

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**Running title**: Excess cancer following $^{211}$At TAT



**ABSTRACT**

Intraperitoneal $^{211}$At-based targeted alpha therapy (TAT) may hold most promise as an adjuvant therapy following surgery and chemotherapy in epithelial ovarian cancer to eradicate any remaining undetectable disease. This implies it will also be delivered to patients possibly already cured by the primary treatment. An estimate of long-term risks is therefore sought whether to justify the treatment. **Methods**: Baseline data for risk estimates of alpha-particle irradiation were collected from published studies on excess cancer induction and mortality for subjects exposed to either $^{224}$Ra treatments or Thorotrast contrast agent (25% $ThO_2$ colloid, containing $^{232}$Th). Organ dosimetry for $^{224}$Ra and Thorotrast irradiation were taken from the literature. These organ-specific risks were then applied for our previously reported dosimetry for intraperitoneal (i.p.) $^{211}$At-TAT patients. **Results**: Risk could be estimated for 10 different organ or organ groups. The calculated excess relative risk per Gray (ERR/Gy) could be sorted into two groups. In the lower ERR/Gy group, up to approx. 5, were: Trachea, bronchus and lung 0.52 (CI 95% 0.21-0.82), Stomach 1.4 (CI 95% -5.0-7.9), Lymphoid and hematopoietic system 2.17 (CI 95% 1.7-2.7), Bone and articular cartilage 2.6 (CI 95% 2.0-3.3), Breast 3.45 (CI 95% -10-17) and Colon 4.5 (CI 95% -3.5-13). In the higher ERR/Gy group, ranging from approx. 10 to 15 were: Urinary bladder 10.1 (CI 95% 1.4-23), Liver 14.2 (CI 95% 13-16), Kidney 14.9 (CI 95% 3.9-26) and Lip, oral cavity and pharynx 15.20 (CI 95% 2.73-27.63). Applying a typical candidate patient (female, age 65 years) and correcting for reference population mortality rate, a total *estimated* excess mortality of an i.p. $^{211}$At-mAb treatment amounted to 1.13 per 100 treated. More than half of this excess originated from urinary bladder and kidney, 0.29 and 0.34 respectively. Depending on various adjustments in calculation and assumptions on competing risks excess

mortality could range from 0.11 – 1.84 per 100 treated. **Conclusion**: Published epidemiological data on life-long detriment following alpha-particle irradiation and its dosimetry allowed calculations to estimate the risk for secondary cancer following $^{211}$At-based i.p. TAT. Measures to reduce dose to the urinary organs may further decrease the estimated relative low risk for secondary cancer from $^{211}$At-mAb based i.p. TAT.

**Key words**: secondary cancer, alpha particle, targeted alpha therapy, human, astatine-211, radium-224, thorium-232, Thorotrast

## INTRODUCTION

Alpha particle emitting radionuclides are evaluated for targeted alpha therapy (TAT). However, estimates of long-term risks, such as for induction of secondary cancer, has not been a priority in the performed early phase studies. This is probably because most patients considered for TAT at this early phase of drug development have late-stage disease where treatment is not aimed at curing the patient.

The combination of high energy and short range makes alpha irradiation most promising for delivering high absorbed dose to target volumes <1 $mm^3$ (*1*). This makes TAT ideal for adjuvant therapy, i.e. following the primary treatment of surgery, radiation therapy and/or pharmacological therapy, where patients are disease free by objective measures but carries a statistical risk of recurrence. Since all use of radiation in medicine must be properly justified, the treatment benefit must outweigh any possible and probable risks. Such justification becomes more delicate for an adjuvant setting where a proportion of the patients are already cured by the primary treatment.

Low organ absorbed doses, well below estimated tolerance doses were found in a phase I study with intraperitoneal (i.p.) delivery of therapeutic amounts of $^{211}$At conjugated to MX35 F(ab')$_2$ ($^{211}$At-mAb) (*2*). No radiation-linked acute toxicity was observed including four patients with 6 – 12 years survival, no other observable side effects were revealed (*3*). As the risk to induce secondary cancer by radiation can be calculated, effective dose for this treatment has been published (*4*). Effective dose is, however, only intended for application in radiation protection and can at best provide a rough estimate of the long-term risk. For alpha-particle irradiation, a conservative radiation weighting factor of 20 is applied, whereby risk might be overestimated. If this leads to overly cautious (e.g., lower) amounts of the therapeutic agent being delivered, then the therapy results might be negatively affected. There is an obvious need for estimating the risk of induction of secondary cancers, particularly for planning further clinical studies in the adjuvant setting, where long-term survival is expected.

In this work, we estimate carcinogenic risks for a novel TAT by comparing resulting organ absorbed doses with the best data available on cancer incidence and mortality from long-term

follow-up of patients who received alpha-emitting substances. By directly calculating risk following alpha irradiation from the known long-term effects of other alpha irradiations, the uncertainty involved in determining a radiation weighting factor for alpha irradiation is eliminated. Published organ-by-organ relative risks for secondary cancer following administration of alpha-emitting compounds Thorotrast (*5-9*) and $^{224}$Ra (*10-12*) were used.

The aim of this work was to compile and evaluate published data relevant to the estimation of carcinogenic risk that could prove useful for justifying adjuvant intraperitoneal TAT. It could also serve as a reasonable method for estimating long-term toxicity also for other TATs.

## MATERIALS AND METHODS

### Background Data

All data used in this study are from published studies or public registers where no individual data can be distinguished. The $^{211}$At-mab study was approved by the Regional Ethical Committee and signature of written informed consent was obtained (*2*).

Only studies with injected alpha-emitting solutions used for medical purpose were included, i.e. excluding environmental exposure studies. Two types of studies were identified as suitable: Follow-up studies of patients who received the $^{232}$Th-containing X-ray contrast medium Thorotrast (*5-9*) and patients who received $^{224}$Ra for the treatment of tuberculosis and ankylosing spondylitis (*10-12*). In all, six Thorotrast series (Table 1) and two $^{224}$Ra-studies (Table 2) were identified. A small overlap of included subjects is reported from the Japanese autopsy study (*8*) (Table 1). We excluded the data on lung cancer from the $^{224}$Ra-studies and from the Thorotrast autopsy study. A lower than expected lung cancer incidence or mortality is reported that is thought to be due to less smoking among the treated patients due to the underlying medical condition as discussed in Wick et al. Nekolla et al. (*10,11*) and Mori et al. (*8*).

To estimate risk, the standardized mortality ratio (SMR), standardized incidence ratio (SIR) or the ratio between observed cases in the exposed group and a control group were extracted

directly or calculated from the studies. Both sexes were included while, where possible, individuals <20 years of age were excluded. All six Thorotrast studies administered similar amounts of Thorotrast (Table 1), but the injected activity of $^{224}$Ra differed pending on the illness treated (Table 2).

In each study excess relative risk per Gray (ERR/Gy) was calculated for the organ sites where absorbed doses was given (Supplemental Table 1). The extracted observed and expected numbers of cancer/deaths per organ and study are presented in Supplemental Table 2. The absorbed doses used are presented in Table 3. Confidence intervals for SIR/SMR/RR were calculated based on a Poisson distribution for counts. For each analyzed organ site, appropriate studies were pooled together and weighted with an inverse-variance approach (*13*). The metan macro for Stata statistical software was used for the pooling calculations (*14*).

The typical candidate being treated with $^{211}$At-mAb for ovarian cancer is a female aged 50-60 years and the lag period for long term risk is assumed to be 10 years. Therefore, cancer site specific mortality rates by 5-year age groups for females aged 65+ in Nordic countries from 2007 to 2016 were derived from Nordcan (*15*). Weighting factors, based on the fraction of the population alive compared to the total population aged 65+, were applied to all-cause mortality rates to account for patients dying of other causes. All-cause mortality data was taken from Statistics Sweden (*16*), for Swedish females aged 65-85+. It was assumed that within each age group, the mortality rate was constant when calculating the weighting factors for each site. The weighting factors can be seen in Supplemental Table 3.

$$m_{w\,65+} = \sum_{i=age\ group} m_i * w_i$$

Equation 1. Calculation for weighted reference population mortality for ages 65+ ($m_{w\,65+}$) for each site, $m_i$ is the site specific mortality for the age group and $w_i$ is the fraction alive in the age group of the total population aged 65+.

**Dosimetry Data**

Absorbed dose to liver following Thorotrast injection were derived from Ishikawa *et al*. (*17*), to bone and bone marrow from Kaul *et al*. (*18*), and to the remainder of organs from Ishikawa *et al*. (*19*), with assumed distributions of radioactive daughters. Absorbed doses following $^{224}$Ra irradiation were taken from Lassman *et al*. (*20*). The resulting absorbed doses used are given in Table 3.

**Outcome**

The excess mortality for each cancer site was calculated from the estimated ERR/Gy for this cancer site from the published epidemiological studies, and multiplied with the dose received in the corresponding organ (Gy) following an i.p. treatment with 200MBq/L $^{211}$At-mAb (*4*) and further multiplied by the weighted reference population mortality rate for this cancer site after 65 years of age ($m_{w\ 65+}$).

$$\text{Excess mortality} = \text{ERR/Gy} * \text{Gy} * m_{w\ 65+}$$

Equation 2. Calculation for Excess mortality

To calculate the total excess mortality from a treatment the results from the different sites were summed up.

**RESULTS**

Published Thorotrast studies were based on 5,870 (69% male, 31% female) patients and the $^{224}$Ra studies comprised 2,153 patients (86% male, 14% female). Thus, the total for both treatment cohorts was 8,023 patients (74% male, 26% female). Median follow-up time was 26 years (range 15 to 55 years). In total 1,638 observed cancer events were used, the excess number of reported cancers were 1,071 and 119 for the Thorotrast and $^{224}$Ra cohorts, respectively. Details of number observed, expected, risk ratio and excess cancer per organ site and per study are presented in Supplemental Table 2. Included studies and patient

characteristics are presented in Table 1 (Thorotrast) and Table 2 ($^{224}$Ra). The calculated absorbed dose data per organ or group of organs are presented in Table 3.

**Excessive Relative Risk per Gray**

The resulting pooled excess relative risk per Gray (ERR/Gy) for the 10 different organs/ organ groups were calculated with 95% confidence interval, and presented in Figure 1. Generally, the 95% confidence interval was wide: Lip, oral cavity and pharynx 15.20 (2.73 - 27.6); Stomach 1.43 (-5.01 - 7.86); Colon 4.53 (-3.95 - 13.01); Breast 3.45 (-10.44 - 17.34); Urinary bladder 10.01 (1.39 - 22.28); Kidney 14.93 (3.94 - 25.92), but narrow for: Trachea, bronchus and lung 0.52 (0.22 - 0.83); Lymphoid and hematopoietic system 2.17 (1.68 - 2.66); Bone and articular cartilage 2.63 (1.97 - 3.30); and Liver 14.20 (12.82 - 15.57). Forest plots demonstrating the ERR/Gy from the respective individual studies and the resulting weighted overall ERR/Gy are found in Supplemental Figure 1 and Supplemental Table 1.

**Excess Mortality**

The resulting excess mortality of cancer induction following an i.p. treatment with 200Mbq/L $^{211}$At-mAb were estimated by multiplying treatment organ dose with the ERR/Gy and with the weighted natural mortality for a typical patient, i.e. female of 65 years, (eq 2). The total expected excess lifetime mortality of the treatment summed up to 1.13 per 100 when applying the most solid background data to derive ERR/Gy i.e. using both male and female observed/expected data. The influence of various assumptions and competing risk is presented in Table 4 and Supplemental Table 4. More than half of the excess cancer mortality were identified as from the urinary bladder (0.29) and the kidney (0.34). The lowest contribution to excess mortality per 100 were from bone and articular cartilage (0.002), and from the lymphoid and hematopoietic system (0.02).

## DISCUSSION

With the introduction of TAT for clinical use, reliable risk estimations of long-term detriment, such as cancer induction are needed to justify the procedure. The alpha particles have a short path length with a high LET (linear energy transfer), that make them an ideal treatment for small-scale malignant disease. Adjuvant treatment in cancer aims at reducing the relapse rate for a cohort of patients subjected to treatment when compared to no treatment. Since only a fraction of these patients will relapse, it follows that the others are cured by the primary therapy. For the latter group, the adjuvant treatment will be of no benefit while carrying a possible risk. Therefore, a shared decision-making process is recommended when proposing an adjuvant therapy to the patient. The risks from all suggested treatments need to be disclosed and be related to the expected gain of the therapy.

Estimation of risk is valuable for at least two reasons: For proper optimization and planning of effect-finding studies, and to provide patients adequate information about possible benefits and risks. To state that the risks are unknown for a radiation-based therapy would not be correct nor ethical. While the risks are uncertain, some estimates would be useful background to discussions with patients prior to their informed consent.

A recent study estimated excess cancer risk from a cohort of almost 150,000 patients following $^{131}$I treatment of well differentiated thyroid cancer. A very small but statistically significant risk of second hematological malignancy was found (*21*). That work initiated a debate on both the necessity and the difficulties involved in performing such excess risk estimates (*22,23*). It is evident that true risk can only be assessed after long follow-up of patients exposed to a specific therapy, preferably in a randomized controlled trial.

We have previously used i.p. infusion of up to 200 MBq/L of $^{211}$At-mAb in a phase-I study resulting in absorbed doses well below tolerance doses (using RBE=5) with low radiation-induced toxicity (*2,3*). Using biokinetic modelling, an activity concentration of 200 MBq/L was assumed sufficient to achieve radical absorbed doses to microtumors (*24*). When we applied the International Commission on Radiological Protection (ICRP)-recommended radiation weighting

factor of 20 for alpha irradiation, the studied patients received an effective dose of 2.6 Sv (*4*) at this activity concentration. This would indicate a life-long lethal cancer risk of around 10%. Effective dose should not, however, be used for any radiotherapy as clearly stated by the ICRP itself (*25*). More specifically, the fundamental weaknesses of the effective dose as applied to alpha irradiation has been thoroughly discussed (*26*). In the present work, we investigated if published literature contained relevant amounts of data to calculate risk directly, i.e. data on epidemiologically derived carcinogenic risk following alpha-particle irradiation.

To do this we selected studies, by focusing on long-term reports of carcinogenic risk following medical use of alpha-particle irradiation, i.e. Thorotrast ($^{232}$Th) (*5-9*) and $^{224}$Ra (*10-12*). These studies from multiple research groups contain well-documented radionuclide exposure to several thousand patients including life-long follow-up. Notably, most reported organ doses for $^{232}$Th and $^{224}$Ra are low and comparable with the organ doses received following adjuvant i.p. TAT with $^{211}$At-labelled antibodies. Contributions from electrons and photons were considered negligible.

Thorotrast was a colloidal suspension of 25% $ThO_2$ (including $^{232}$Th) used as injectable contrast agent in the 1930s-40s (*27*). The long biological half-life resulted in life-long irradiation (*28*) and lifetime doses of several gray (Gy) were received in reticuloendothelial organs with a resulting clear excess risk of cancers (*17*). Approximately 5% of the $^{232}$Th will distribute to other tissues with absorbed doses of 0.01 – 0.1 Gy (*19*), where cancer excess is not always statistically significant, but is included in this combined analysis. The strength of the dose calculations for Thorotrast lies in the use of actual measured thorium concentrations, in several tissues, from a reasonable number of individuals, while the main uncertainty lies in estimating the contribution from $^{232}$Th daughters (*17,19*).

$^{224}$Ra-radium chloride, as a component of Peteosthor, was used to treat bone tuberculosis or ankylosing spondylitis until the early 2000s (*11*). Its use for the treatment of children and juveniles suffering from bone tuberculosis was stopped in 1956 due to the reported growth

retardation and excess occurrence of bone sarcomas (*29*). The amount of $^{224}$Ra radioactivity administered up to that time was approximately 50 MBq in the "high-dose" treatment. Thereafter activity was reduced to about 10 MBq for treatment of ankylosing spondylitis in young adults. For the $^{224}$Ra dosimetry we used data from Lassman *et al*. (*20*) that are based on the age-dependent biokinetic model for alkaline earth elements as described in ICRP Publication 67 (*30*). In the current work, we have excluded patients <20 years, but the mean age of remaining patients is still comparatively low at 37 years. The mean latency time for $^{224}$Ra induced bone cancer was reported to be approximately 15 years (*31*). For other malignancies, the mean latency times were approximately 25 years, though presented with large uncertainty (*10,11*).

The ovarian cancer patients intended for an i.p. $^{211}$At-mAb therapy have a median age of 63, which is clearly higher than those exposed to Thorotrast and $^{224}$Ra (33 and 37 years, respectively). For low-LET irradiation, the age dependence is not trivial (*32*). Although latency is generally long, the risk reduction by age at irradiation is not noticeable until approximately 65 years of age. The exceptions are breast and bone cancer where risk reduction is seen already at age 50 at the time of irradiation (*33*). If a similar age dependence as for low-LET radiation also applies for $^{211}$At-mAb treated patients, the risk for breast and bone cancer (excess 0.036 and 0.002 per 100 treated, respectively) could be reduced by approximately a factor of two. However, since such data does not exist for high-LET irradiation, the main result of 1.13 excess cancer per 100 treated is without any age correction. Moreover, a younger patient has a longer life expectancy compared to an older patient (of same disease stage) and thereby a higher risk to be diagnosed with a secondary cancer. We adjusted the background mortality-rate data used accordingly with a resultant risk decrease with higher age at treatment. In Table 4 only the excess cancer numbers for 25 and 65 years are presented, but detailed in Supplemental Table 5.

In Table 4, the effects of making different assumptions or adding competing risks can be seen, all results are presented as 'number of excess cancer per 100 treated' (with 200 MBq/L $^{211}$At-mAb i.p.). For example in the analyzed cohorts (Table 1 and 2) female sex only constituted

approximately 25% of all individuals. Two studies (*5,10*) contained some data grouped by sex. If only the female data were used to calculate the ERR/Gy the number of excess cancer for a cancer-free female of 55 year amounted to 1.60. We find this number more uncertain as the female only derived ERR/Gy is based on much fewer observed cancer cases with a resultant much wider CI (Supplemental Table 4). Additionally, we demonstrate the effect of two kinds of competing risks. First, ovarian cancer stage is correlated to mortality, i.e. a patient in FIGO stage IV is more likely to die from ovarian cancer before developing a secondary cancer. Therefore, the excess cancer cases decrease when adjusting for the survival of ovarian cancer as shown for FIGO stages I to IV (Table 4). Secondly, patients surviving ovarian cancer are at increased risk of a second primary cancer, compared to the normal population (*34*). To account for this the excess cancer cases are multiplied with the hazard ratios for the risk to be diagnosed with a second primary cancer following an ovary cancer diagnosis (*34*). This results in an increase from 1.13 to 1.53 per 100 treated 'cancer-free' patients, no adjustment for decreased survival due to the secondary cancer was done, Table 4 and Supplemental Table 4.

The use of cancer excess data following exposure of $^{232}$Th and $^{224}$Ra are not ideal because of the different half-lives and biological distribution of these alpha-emitters. Also the micro distribution of decays within each organ will likely differ. On the other hand, they provide the best clinical data available for estimating long-term risk following alpha-particle therapies because the studies include solid data for some 8,000 patients with often life long-follow-up. In our estimates we have assumed that the risk is a linear function of the organ mean absorbed dose. This implies a linear no-threshold model. This presumption is reasonable if cancer induction originates from one stochastic mutation induced by an alpha particle traversing the cell nucleus (*26*). A deviation from linearity may be expected when high radiation doses are received under a short time, since an increased likelihood for cell death will reduce the cancer induction risk. For $^{232}$Th, several observations indicate risk increasing linearly with increasing dose. This includes the liver that receives the highest absorbed dose with a very heterogeneous dose distribution (*35*). Using a two-mutation carcinogenesis model the conclusion was that the excess absolute risk for liver tumors correlate linearly with absorbed dose (*36*).

The resulting highest excess cancer contribution were from urinary bladder and from kidney. However, diuretics and an open indwelling urinary catheter to reduce transit time can decrease the dose to the bladder, and probably the dose to kidney. It is also likely that $^{211}$At-compounds with improved in vivo stability can reduce risk to organs associated with uptake of free $^{211}$At.

**CONCLUSION**

Relevant data in published literature was found that allowed carcinogenic risk estimation. The results presented herein should be viewed as a first estimate of long-term risk for cancer induction following i.p. alpha particle treatment. They carry uncertainties in both the presented excess cancer incidence and dosimetry, while still representing the best risk estimations available today. Application of this method will strengthen the risk-benefit analysis for patient selection and provides valuable information on organ(s) where we might expect to experience the largest effect of dose optimizations.

**KEY POINTS**

QUESTION: Can risk of secondary cancer following an adjuvant i.p. $^{211}$At-mAb-based therapy be estimated?

PERTINENT FINDINGS: Using organ dose from $^{211}$At, organ-specific risks were estimated from literature data on excess cancer for subjects medically exposed to other alpha-particle emitters ($^{224}$Ra or $^{232}$Th). The excess relative risk was applied for i.p. $^{211}$At-TAT patients, and the total excess mortality could amount to range from 0.1 – 1.8 per 100 treated, depending on various background data or assumptions of competing risks.

IMPLICATIONS FOR PATIENT CARE: The estimation of carcinogenic risk is valuable for proper justification, optimization, and planning of effect-finding studies in forthcoming adjuvant therapy trials, and to provide patients with adequate information about possible benefits and risks.

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FIGURE 1

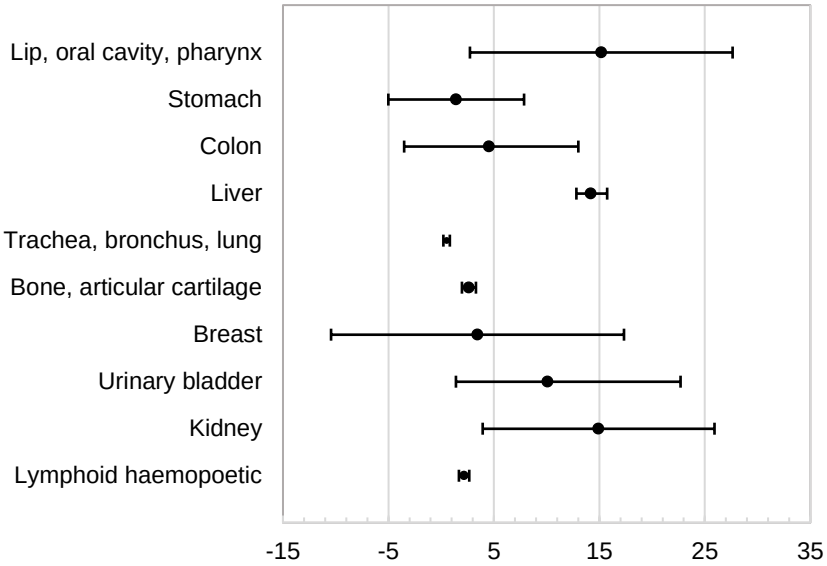



**Figure 1.** Pooled excess relative risk per Gray (ERR/Gy) for the different organs/ organ groups with 95% confidence interval (CI). The data for Bladder represent only one background study, Nekolla et al. 2009 (*10*).

**TABLE 1**
Background Thorotrast data

| Author/year | Study design/ Statistical method | N | Gender N (%) | Age Mean (years) | Comparison group | Estimate Dosage ml * | Exclusion criteria | Last follow-up | Follow-up time (years) | Alive at analysis | Excess cancers | Excess per 100 subjects | Expected number of cancers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Becker 2008 Germany (*5*)** | Site specific Mortality/ SMR | 2326 | M: 1717 (74%) F: 602 (26%) | 31 | 1890 | Mean 21 | Survival <3 years† | 2005 | Mean 34 | 2% | 349 | 15 | 114 |
| **Travis 2003 Sweden/ Denmark (*9*)** | Site specific incidence/SIR and RR | 1204 | M: 670 (56%) F: 534 (44%) | 35‡ | 1180 | Mean 17 | Survival <2 years† | 1992 - 93 | Mean 22 | 7% | 229 | 19 | 77 |
| **Travis 2003 USA (*9*)** | Site specific Mortality/ SMR and RR | 446 | M: 223 (51%) F: 216 (49%) | 41‡ | 212 | Mean 25 | Survival <2 years† | 1992 | Mean 20 | 10% | 50 | 11 | 18 |
| **Dos Santos Silva 2003 Portugal (*6*)** | Site specific Mortality/SMR and RR | 1096 | M: 685 (62.5%) F: 411 (37.5%) | 35‡ | 1014 | Median 20 | Survival <5 years† | 1996 | Mean 15 | 6% | 86 | 8 | 5 |
| **Mori 1999 Japan (*8*)** | Site specific Mortality/ RR | 262§ | M: 262 (100%) | 25 | 1630 | Mean 17 | Survival <10 years† | 1998 | - | 7% | 79 | 30 | 30 |
| **Kido 1999 Japan (*7*)** | Site specific Mortality | 150‖ | M: 150 (100%) | 22 | 1144 | 10-19 ml (94%) | Dead before 1979 | 1998 | - | 12% | 63 | 42 | 8 |
| **Mori 1999 Japan (*8*)** | Autopsy study | 386 | M: 348 (90%) F: 38 (10%) | 9-47 (range) | 172350 | Mean 18 | Survival <10 years† | 1998 | Mean 38 SD 9 | - | 214 | 55 | 105 |

N, number of patients. M, male sex. F, female sex. SD, standard deviation. SMR, standardized mortality ratio. SIR, standardized incidence ratio.

* Thorotrast dosage refers to the volume (ml) of thorotrast injected.

†From Thorotrast injection.

‡Estimated age. §61 and ‖69 patients included in the Autopsy study, (*8*).

**TABLE 2**

Background $^{224}Ra$ data

| Author/year | Study design/ Stat. method | N | Gender N (%) | Age Mean | Comparison group | Estimated Activity MBq | Exclusion criteria | Last follow -up | Follow-up time (years) | Alive at analysis | Excess cancers | Excess per 100 subjects | Expected number of cancers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nekolla 2010 Germany (*10*)** | Site specific incidence/ SIR | 682 | M: 510 (75%) F: 172 (25%) | * | no | Approx. 45 | Age ≤ 20 years (full cohort n=899). ‡ lag time | 2007 | ~55 | 6% | 92 † | 13 † | 56 † |
| **Wick 2009 Germany (*11*)** | Site specific incidence/ SIR and RR | 1471 | M: 1332 (91%) F: 139 (9%) | * | 1324 | Approx. 10 (0,17/kg) | | | Mean 26 | 32% | 23 † | 0.3 | 159 |

N, number of patients. M, male sex. F, female sex. SMR, standardized mortality ratio. SIR, standardized incidence ratio.

*Mean age not possible to calculate reported as < or > than 20 years.

†Lung cases not included.

‡The Nekolla 2010 study used a 5-year and 2-year lag time for solid tumors and hematological malignancies, respectively.

**TABLE 3**

Calculated absorbed dose data and background natural mortality

| **Organ /group of organs** | **ICD-10 code** | **†Thorotrast** (mGy) | **‡ $^{224}$Ra high** (mGy) | **§ $^{224}$Ra low** (mGy) | **‖ $^{211}$At** (mGy) | **¶ Mortality per 100,000 in female aged 65 +** |
|---|---|---|---|---|---|---|
| Lip, oral cavity, pharynx | C00 – C13 | 174 | - | - | 280 | 36,9 |
| Stomach | C16 | 39 | 99 | 22 | 160 | 80 |
| *Colo-rectum, anal | C18 – C21 | 42 | 297 | - | 36 | 397,2 |
| Liver, intrahepatic bile ducts | C22 | 6900 | 585 | 130 | 104 | 69,6 |
| Trachea, broncus, lung | C33 – C34 | 1094 | 99 | 22 | 320 | 570,5 |
| Bone and articular cartilage | C40 – C41 | 4800 | 19800 | - | 182 | 3,8 |
| Breast (female) | C50 | - | 99 | 22 | 28 | 373 |
| Kidney | C64 – C65 | 45 | 333 | 74 | 340 | 67,3 |
| Urinary bladder | C67 | - | 99 | - | 380 | 76,2 |
| Lymphoid, hematopoietic and related tissues | C81 – C96 | 2100 | 1890 | 420 | 30 | 281,9 |

-, dose data not available.

*Colon (C18-19) 70%, rectum (C20) ~30%.

†Thorotrast mean administered 20ml and mean 30 years exposition using distribution data from Ishikawa *et al*. (*17,19*)

‡$^{224}$Ra 45 MBq (high) and § $^{224}$Ra 10 MBq (low), applied to distribution from Lassman *et al*. (*20*).

‖$^{211}$At 200 MBq/L in i.p. infusion, 24 hrs. dwell time, from Cederkrantz *et al*. (*4*).

¶Mortality data from Nordcan (*15*) weighted by the natural mortality in the age span, data from Statistics Sweden (*16*).

**TABLE 4**

Influence of Various Assumptions and Competing risk*

| Adjustment in calculation or used background | | Excess cancer cases per 100 treated † | | | | |
|---|---|---|---|---|---|---|
| | | Cancer free | FIGO stage* | | | |
| | | | I | II | III | IV |
| Using ERR/Gy based on 'Male and female' ‡ | | 1.13 | 0.90 | 0.64 | 0.25 | 0.11 |
| Using ERR/Gy based on 'Female sex only' § | | 1.60 | 1.28 | 0.91 | 0.35 | 0.16 |
| Age dependence adjustment ‡<br>If low LET equals high LET, | | 1.11 | 0.89 | 0.63 | 0.24 | 0.11 |
| Other 2nd cancer risk following an Ovarian Cancer primary, k ‡ | | 1.53 | 1.24 | 0.87 | 0.34 | 0.15 |
| Age (*25 or 65 year)* at time of treatment ¶ | ERR/Gy 'Male and female' ‡ | 1.24 – 0.90 | | | | |
| | ERR/Gy 'Female sex only' § | 1.84 – 1.21 | | | | |

*10 year ovarian cancer relative survival according to FIGO (International Federation of Gynecology and Obstetrics) stage I – IV (0.80 / 0.57 / 0.22 / 0.11), (*37*).

†Female patients, 55 year at treatment.

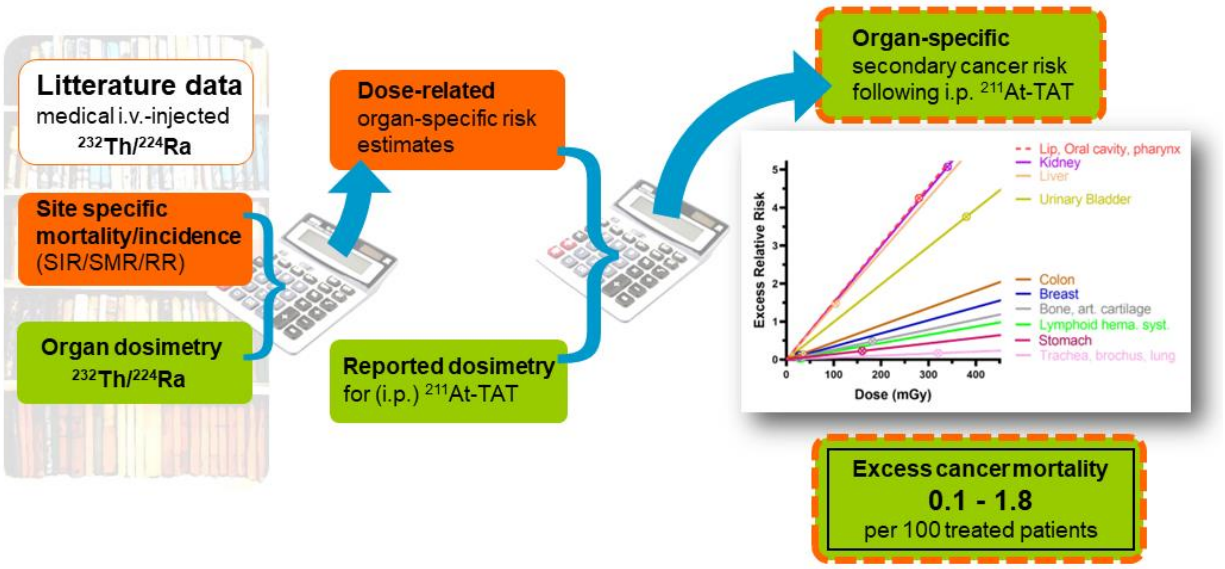
‡Calculations made with the 'Male and female' derived ERR/Gy in Supplemental Table 4.

§Using ERR/Gy based on 'Female only'.

kHazard risks (*34*), specified in Supplemental Table 4. No adjustment for decreased survival due to the second primary cancer is performed.

¶The influence of 'age at treatment' (25 and 65 years) is presented, specified in Supplemental Table 5.

**Graphical Abstract**



## SUPPLEMENTAL FIGURE 1A – 1J

Forest plots demonstrating the Excessive Relative Risk per Gray (ERR/Gy) from the respective individual studies and the resulting weighted overall EER/Gy.

Note

- In Figure 1A (Lip oral cavity and pharynx), the ERR/Gy is based only on Thorotrast data as there are no $^{224}$Ra dose data available.

- Figure 1B (Stomach); 1C (Colon); 1D (Liver and intrahepatic bile ducts); 1G (Bone and articular cartilage); 1I (Kidney) and 1J (Lymphoid, hematopoietic and related tissues) are based on data from both Thorotrast and $^{224}$Ra studies.

- Figure 1E (Trachea, bronchus and Lung) is presented with all $^{224}$Ra-studies excluded and the Thorotrast autopsy study (Mori 1999) excluded due to bias from different smoking habits as discussed in main article. For reference we present Figure 1F (Trachea, bronchus and Lung) a forestplot were the $^{224}$Ra studies and the Mori autopsy study are included.

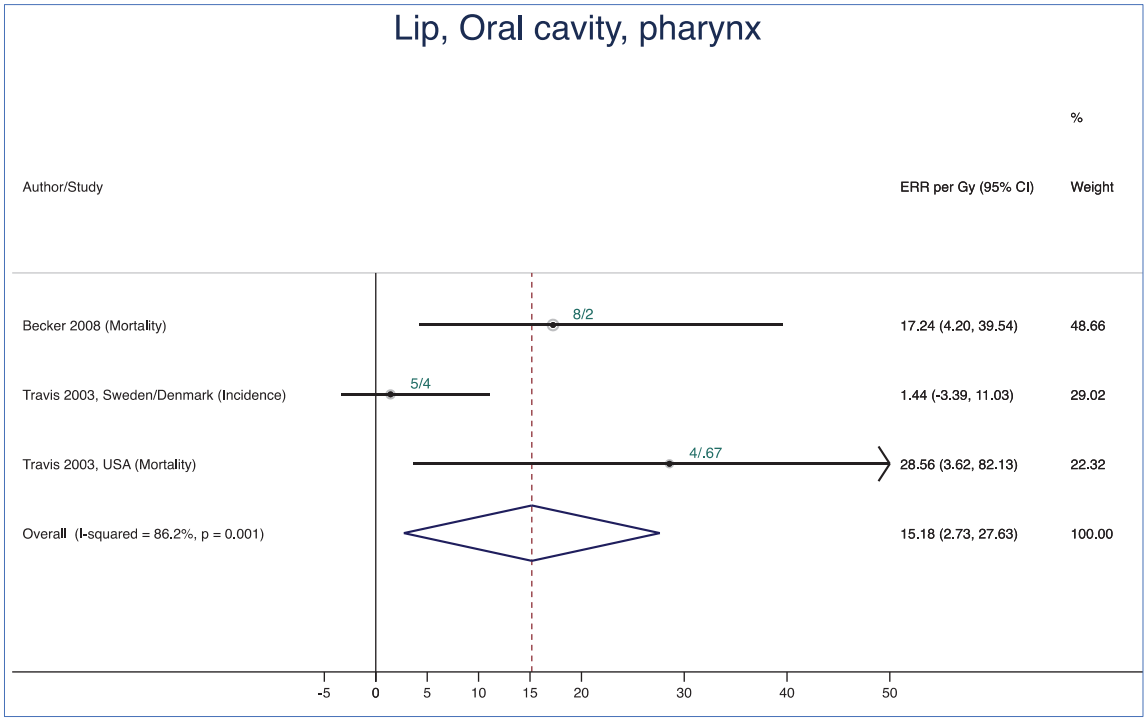
- Figure 1H (Breast) is based only on $^{224}$Ra data, as no dose data for breast is available for thorium.

- No pooling, with demonstrating Forest plot is done for Bladder as only one data point is available (Nekolla 2010):

### Urinary Bladder:

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Nekolla 2010 | 10.10 | 1.40 | 22.20 | 100.00 |

## Sup. Figure 1A , Lip oral cavity and pharynx



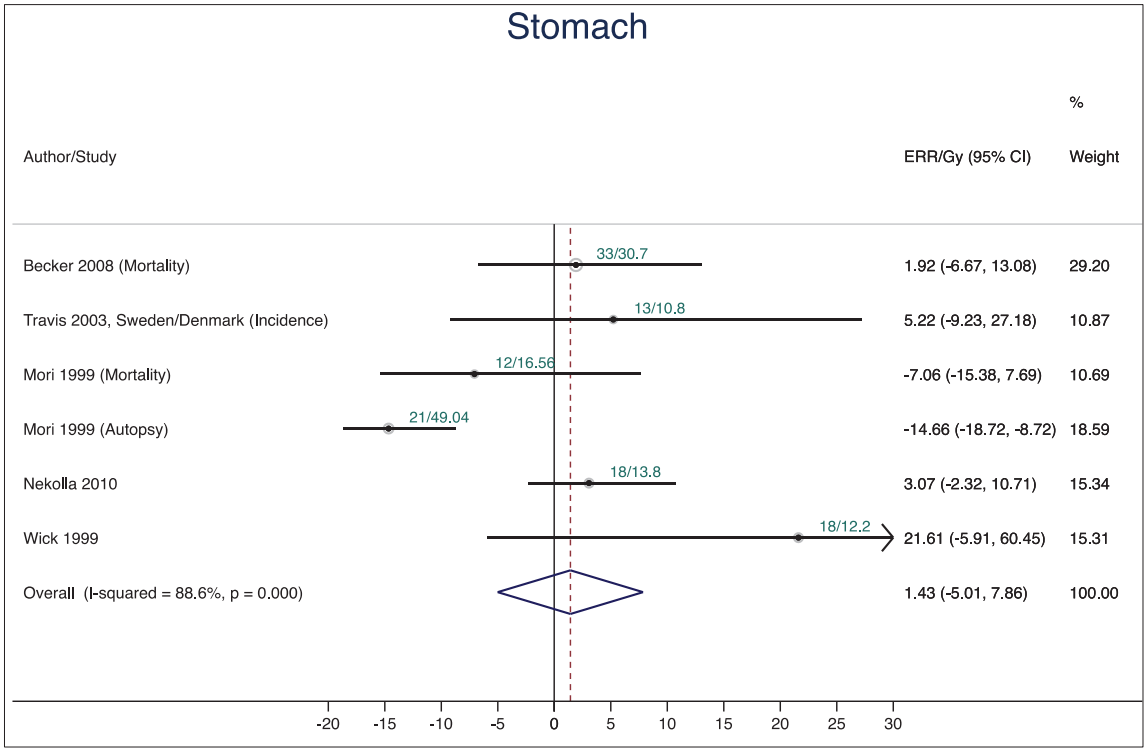

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 17.241 | 4.195 | 39.540 | 48.66 |
| Travis 2003, Sweden/ | 1.437 | -3.391 | 11.034 | 29.02 |
| Travis 2003, USA (Mo | 28.563 | 3.621 | 82.126 | 22.32 |
| * pooled ES | 15.182 | 2.728 | 27.635 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  14.45 (d.f. = 2) p = 0.001
  I-squared (variation in ES attributable to heterogeneity) =  86.2%

  Test of ES=0 : z=   2.39 p = 0.017
```

## Sup. Figure 1B, Stomach



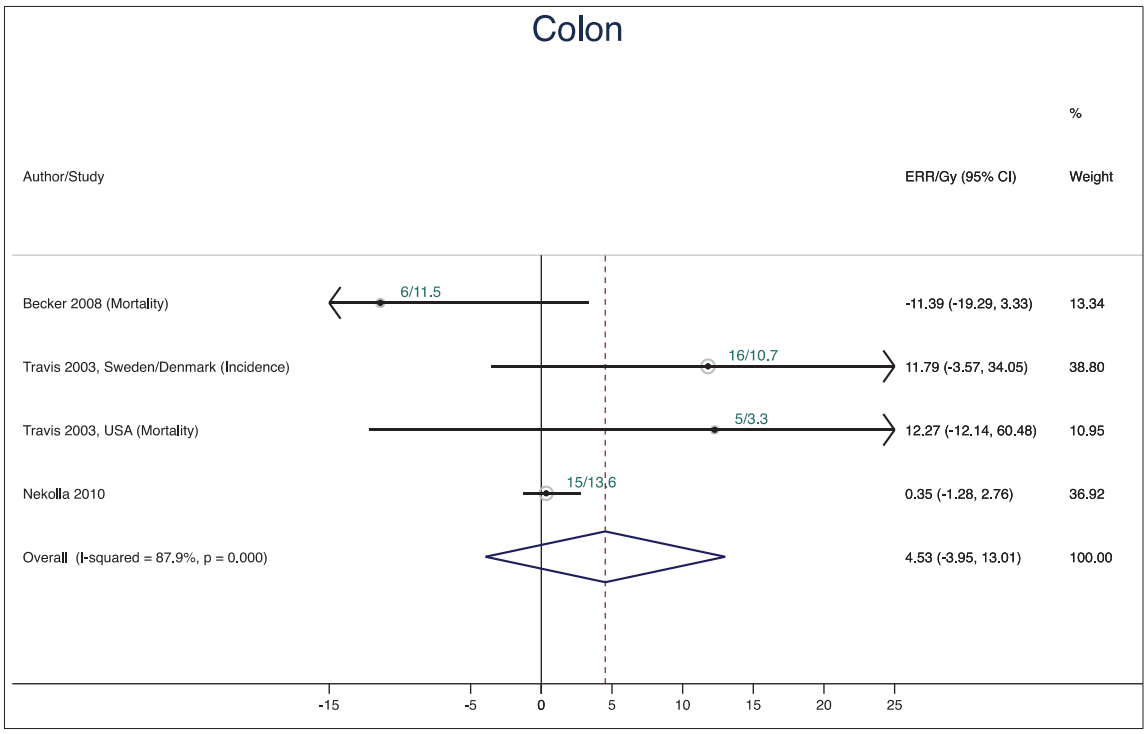

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 1.921 | -6.667 | 13.077 | 29.20 |
| Travis 2003, Sweden/ | 5.223 | -9.231 | 27.179 | 10.87 |
| Mori 1999 (Mortality | -7.061 | -15.385 | 7.692 | 10.69 |
| Mori 1999 (Autopsy) | -14.661 | -18.718 | -8.718 | 18.59 |
| Nekolla 2010 | 3.074 | -2.323 | 10.707 | 15.34 |
| Wick 1999 | 21.610 | -5.909 | 60.455 | 15.31 |
| * pooled ES | 1.427 | -5.008 | 7.862 | 100.00 |

* note: trials pooled by user defined weight weight
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 43.69 (d.f. = 5) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 88.6%

Test of ES=0 : z= 0.43 p = 0.664

## Sup. Figure 1C, Colon



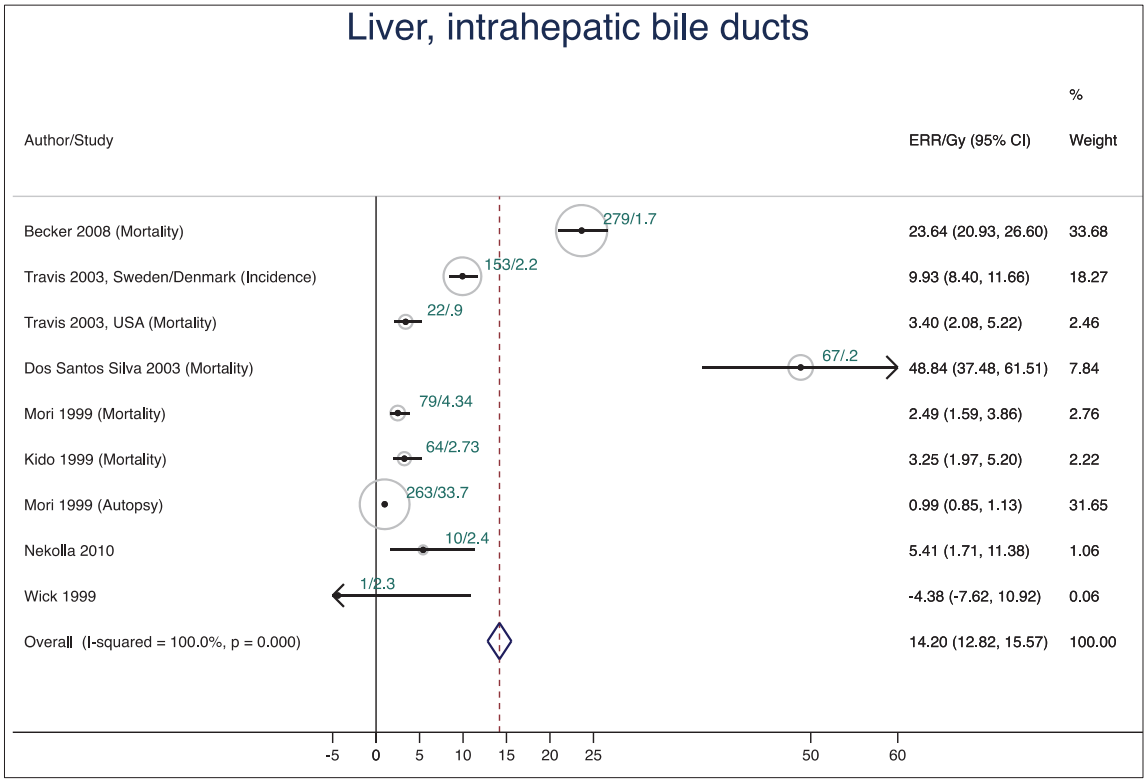

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | -11.387 | -19.286 | 3.333 | 13.34 |
| Travis 2003, Sweden/ | 11.794 | -3.571 | 34.048 | 38.80 |
| Travis 2003, USA (Mo | 12.266 | -12.143 | 60.476 | 10.95 |
| Nekolla 2010 | 0.347 | -1.279 | 2.761 | 36.92 |
| * pooled ES | 4.528 | -3.951 | 13.007 | 100.00 |

* note: trials pooled by user defined weight weight
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 24.81 (d.f. = 3) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 87.9%

Test of ES=0 : z= 1.05 p = 0.295

## Sup. Figure 1D, Liver and intrahepatic bile ducts



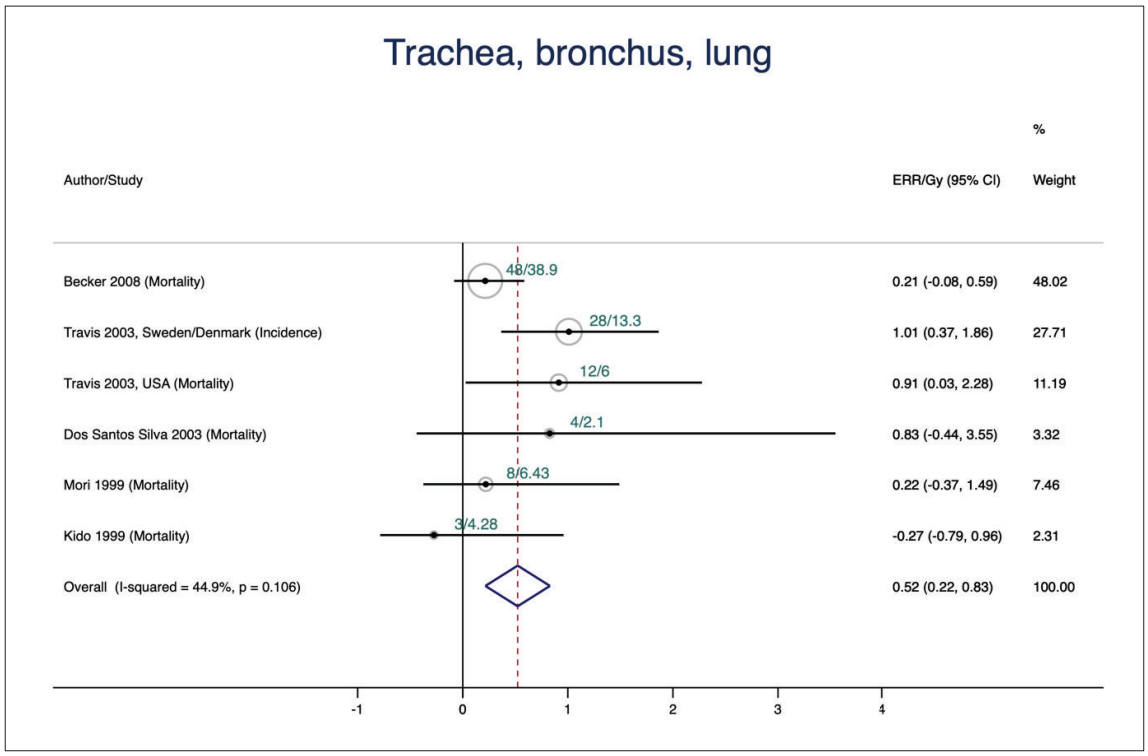

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 23.640 | 20.930 | 26.601 | 33.68 |
| Travis 2003, Sweden/ | 9.934 | 8.400 | 11.664 | 18.27 |
| Travis 2003, USA (Mo | 3.398 | 2.075 | 5.219 | 2.46 |
| Dos Santos Silva 200 | 48.841 | 37.478 | 61.507 | 7.84 |
| Mori 1999 (Mortality | 2.493 | 1.594 | 3.855 | 2.76 |
| Kido 1999 (Mortality | 3.254 | 1.971 | 5.203 | 2.22 |
| Mori 1999 (Autopsy) | 0.986 | 0.854 | 1.132 | 31.65 |
| Nekolla 2010 | 5.414 | 1.709 | 11.385 | 1.06 |
| Wick 1999 | -4.385 | -7.615 | 10.923 | 0.06 |
| * pooled ES | 14.197 | 12.820 | 15.574 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared = 35532.41 (d.f. = 8) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) = 100.0%

  Test of ES=0 : z=  20.21 p = 0.000
```

## Sup. Figure 1E, Trachea, bronchus and Lung (with $^{224}$Ra-studies and Mori- autopsy excluded)



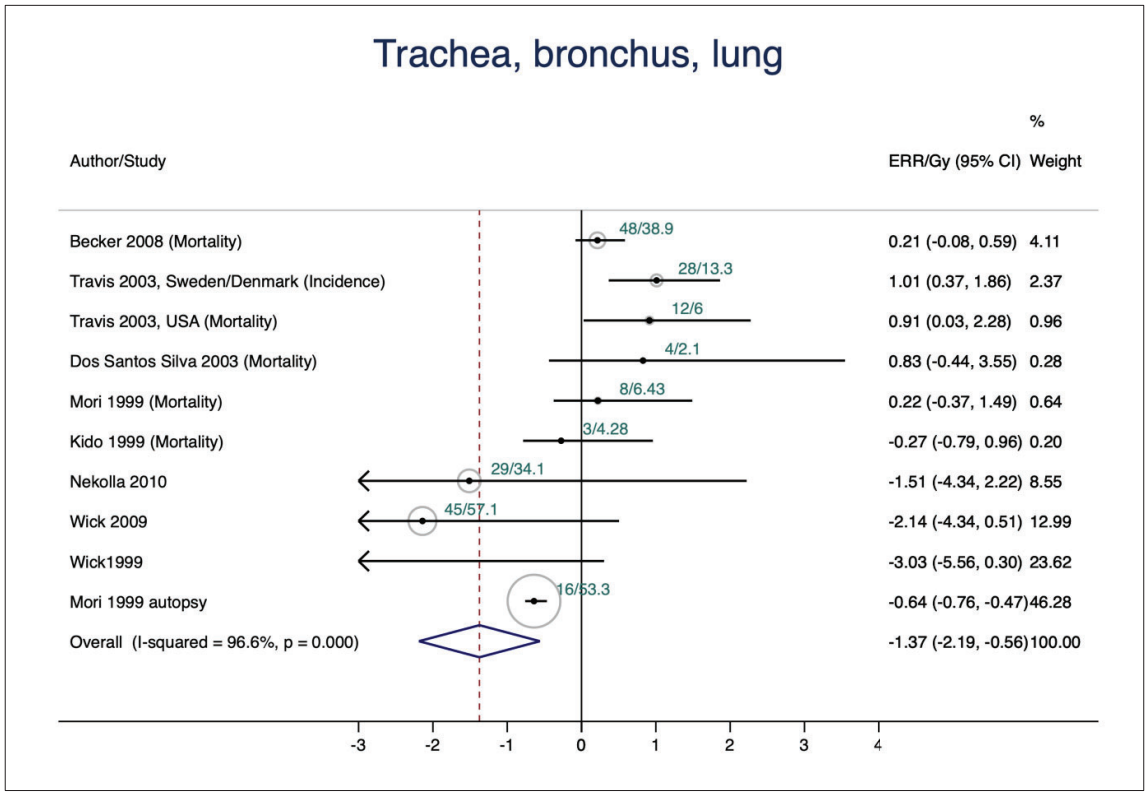

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 0.214 | -0.082 | 0.585 | 48.02 |
| Travis 2003, Sweden/ | 1.010 | 0.366 | 1.865 | 27.71 |
| Travis 2003, USA (Mo | 0.914 | 0.027 | 2.276 | 11.19 |
| Dos Santos Silva 200 | 0.827 | -0.439 | 3.547 | 3.32 |
| Mori 1999 (Mortality | 0.219 | -0.375 | 1.490 | 7.46 |
| Kido 1999 (Mortality | -0.274 | -0.786 | 0.960 | 2.31 |
| * pooled ES | 0.522 | 0.215 | 0.829 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   9.07 (d.f. = 5) p = 0.106
  I-squared (variation in ES attributable to heterogeneity) =  44.9%

  Test of ES=0 : z=   3.34 p = 0.001
```

## Sup. Figure 1F, Trachea, bronchus and Lung ($^{224}$Ra-studies and Mori autopsy included)



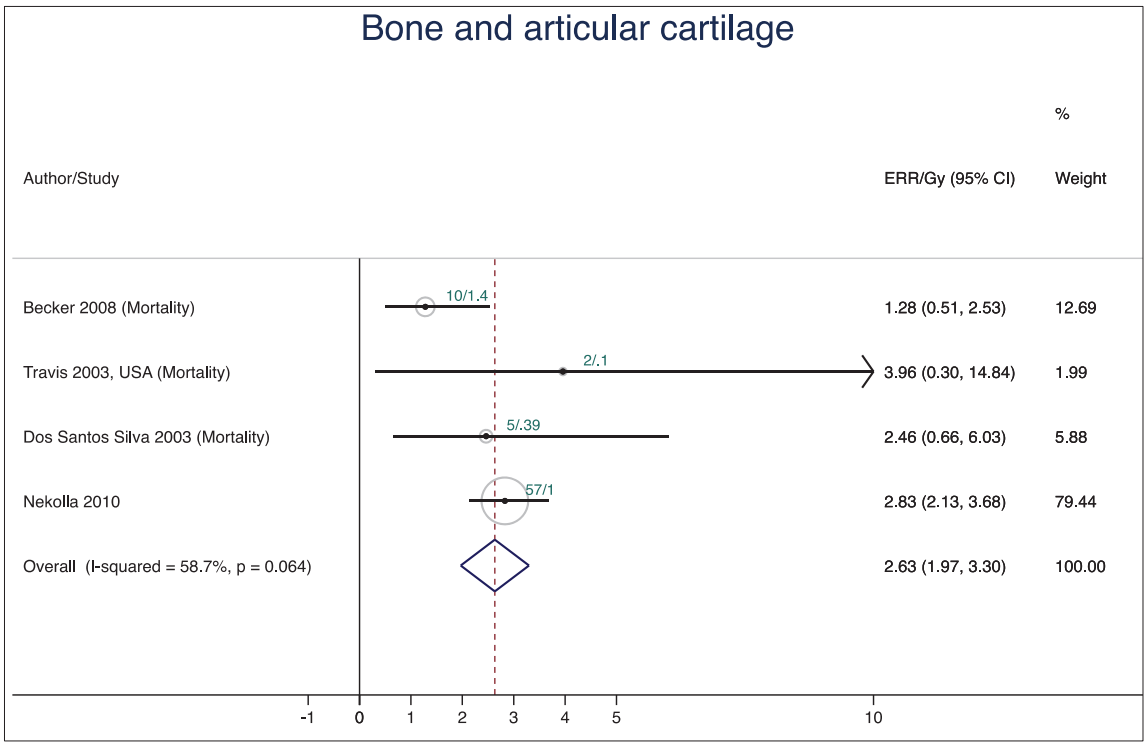

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 0.214 | -0.082 | 0.585 | 4.11 |
| Travis 2003, Sweden/ | 1.010 | 0.366 | 1.865 | 2.37 |
| Travis 2003, USA (Mo | 0.914 | 0.027 | 2.276 | 0.96 |
| Dos Santos Silva 200 | 0.827 | -0.439 | 3.547 | 0.28 |
| Mori 1999 (Mortality | 0.219 | -0.375 | 1.490 | 0.64 |
| Kido 1999 (Mortality | -0.274 | -0.786 | 0.960 | 0.20 |
| Nekolla 2010 | -1.511 | -4.343 | 2.222 | 8.55 |
| Wick 2009 | -2.140 | -4.343 | 0.505 | 12.99 |
| Wick1999 | -3.027 | -5.556 | 0.303 | 23.62 |
| Mori 1999 autopsy | -0.640 | -0.759 | -0.466 | 46.28 |
| * pooled ES | -1.374 | -2.187 | -0.560 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared = 262.17 (d.f. = 9) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  96.6%

  Test of ES=0 : z=   3.31 p = 0.001
```

## Sup. Figure 1G, Bone and articular cartilage



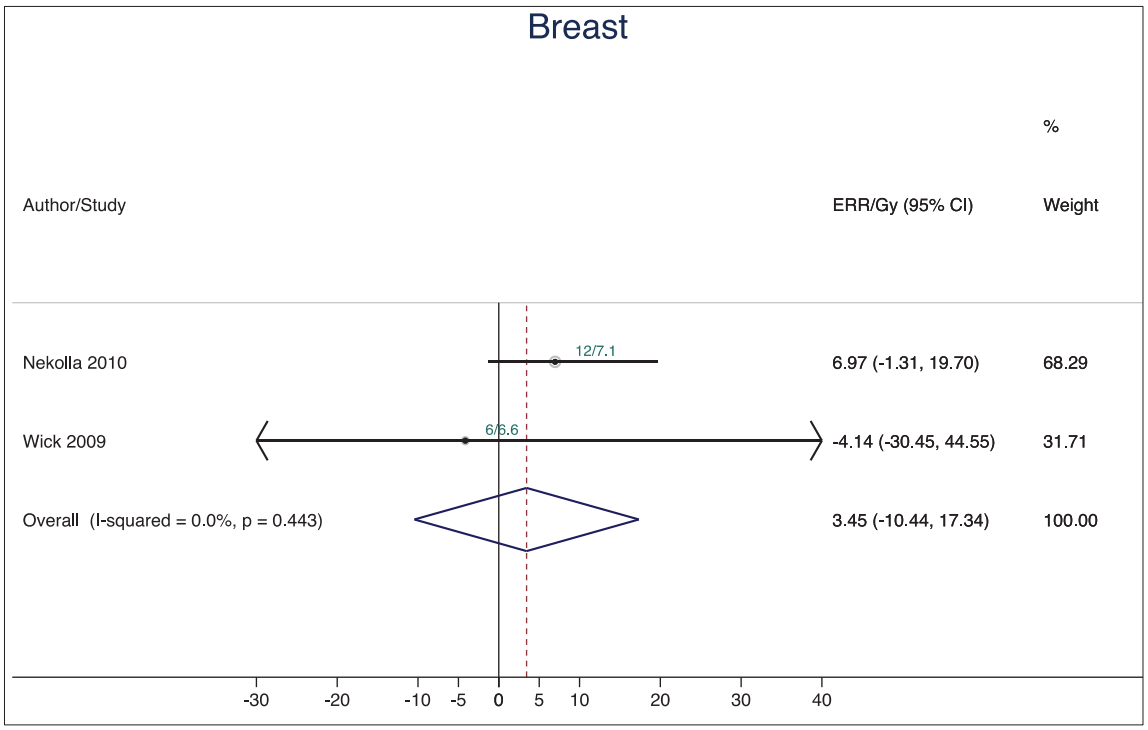

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 1.280 | 0.506 | 2.529 | 12.69 |
| Travis 2003, USA (Mo | 3.958 | 0.296 | 14.844 | 1.99 |
| Dos Santos Silva 200 | 2.463 | 0.658 | 6.025 | 5.88 |
| Nekolla 2010 | 2.828 | 2.130 | 3.679 | 79.44 |
| * pooled ES | 2.633 | 1.969 | 3.297 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   7.26 (d.f. = 3) p = 0.064
  I-squared (variation in ES attributable to heterogeneity) =  58.7%

  Test of ES=0 : z=   7.77 p = 0.000
```

## Sup. Figure 1H, Breast



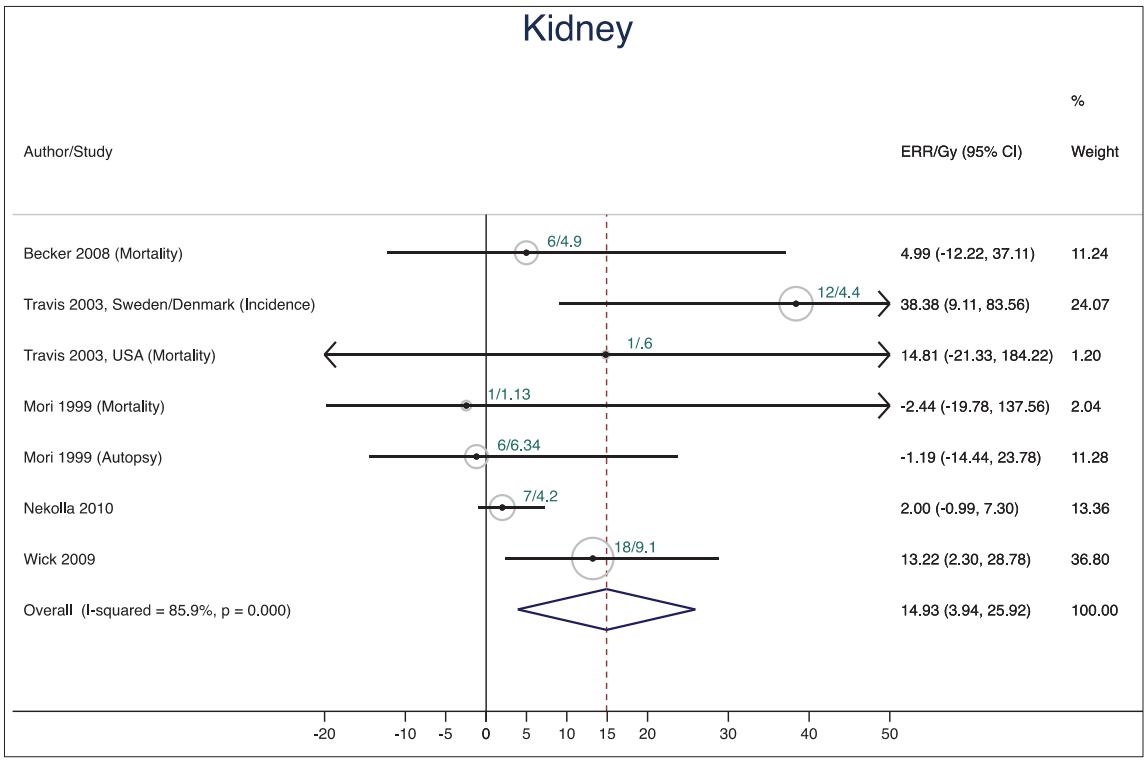

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Nekolla 2010 | 6.970 | -1.313 | 19.697 | 68.29 |
| Wick 2009 | -4.136 | -30.455 | 44.545 | 31.71 |
| * pooled ES | 3.448 | -10.441 | 17.336 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   0.59 (d.f. = 1) p = 0.443
  I-squared (variation in ES attributable to heterogeneity) =   0.0%

  Test of ES=0 : z=   0.49 p = 0.627
```

## Sup. Figure 1I, Kidney



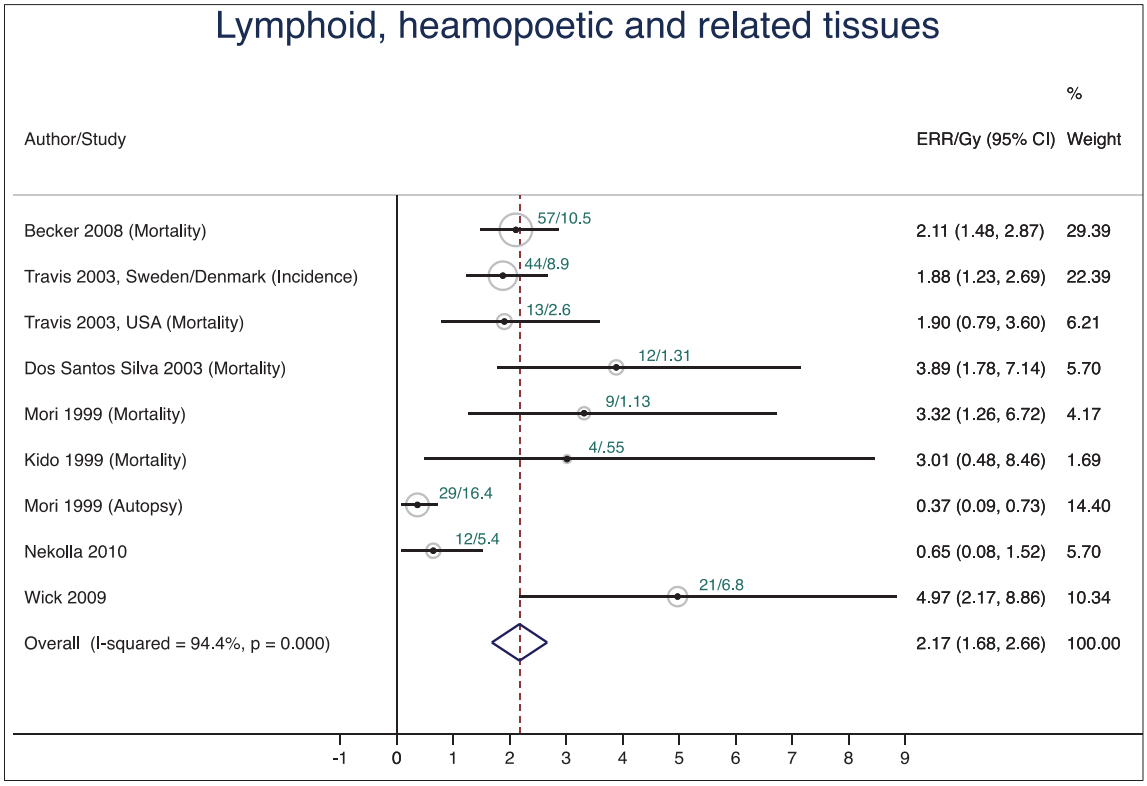

| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 4.989 | -12.222 | 37.111 | 11.24 |
| Travis 2003, Sweden/ | 38.384 | 9.111 | 83.556 | 24.07 |
| Travis 2003, USA (Mo | 14.815 | -21.333 | 184.222 | 1.20 |
| Mori 1999 (Mortality | -2.444 | -19.778 | 137.556 | 2.04 |
| Mori 1999 (Autopsy) | -1.192 | -14.444 | 23.778 | 11.28 |
| Nekolla 2010 | 2.003 | -0.991 | 7.297 | 13.36 |
| Wick 2009 | 13.216 | 2.297 | 28.784 | 36.80 |
| * pooled ES | 14.926 | 3.936 | 25.917 | 100.00 |

* note: trials pooled by user defined weight weight
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 42.49 (d.f. = 6) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 85.9%

Test of ES=0 : z= 2.66 p = 0.008

## Sup. Figure 1J, Lymphoid, hematopoietic and related tissues




| Study | ES | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Becker 2008 (Mortali | 2.109 | 1.481 | 2.871 | 29.39 |
| Travis 2003, Sweden/ | 1.878 | 1.233 | 2.686 | 22.39 |
| Travis 2003, USA (Mo | 1.905 | 0.790 | 3.595 | 6.21 |
| Dos Santos Silva 200 | 3.886 | 1.776 | 7.143 | 5.70 |
| Mori 1999 (Mortality | 3.316 | 1.257 | 6.724 | 4.17 |
| Kido 1999 (Mortality | 3.014 | 0.476 | 8.457 | 1.69 |
| Mori 1999 (Autopsy) | 0.366 | 0.086 | 0.733 | 14.40 |
| Nekolla 2010 | 0.647 | 0.078 | 1.525 | 5.70 |
| Wick 2009 | 4.972 | 2.167 | 8.857 | 10.34 |
| * pooled ES | 2.173 | 1.683 | 2.663 | 100.00 |

```
* note: trials pooled by user defined weight weight
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared = 142.69 (d.f. = 8) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  94.4%

  Test of ES=0 : z=   8.69 p = 0.000
```

## SUPPLEMENTAL TABLE 1

Study specific Calculated Excess Relative Risk per Gray (**ERR/Gy***)
Excess mortality per 100 for a treatment with 200 MBq/L $^{211}$At-mAb

| Organ/ Organsystem | Study | Excess Relative Risk per Gy | Lower CI | Upper CI | Dose $^{211}$At-mAb (Gy) | Mortality per 100 | Excess mortality per 100 |
|---|---|---|---|---|---|---|---|
| Lip, oral cavity, pharynx | Becker | 17.24 | 4.19 | 39.54 | | | |
| | Travis (Swe/Dan) | 1.44 | -3.39 | 11.03 | | | |
| | Travis (USA) | 28.56 | 3.62 | 82.13 | | | |
| | *Pooled* | *15.18* | *2.73* | *27.64* | 0.28 | 0.037 | 0.16 |
| Stomach | Becker | 1.92 | -6.67 | 13.08 | | | |
| | Travis (Swe/Dan) | 5.22 | -9.23 | 27.18 | | | |
| | Mori (Serie 1) | -7.06 | -15.39 | 7.69 | | | |
| | Mori (autopsy) | -14.66 | -18.72 | -8.72 | | | |
| | Nekolla | 3.07 | -2.32 | 10.71 | | | |
| | Wick 1999 | 21.61 | -5.91 | 60.46 | | | |
| | *Pooled* | *1.43* | *-5.01* | *7.86* | 0.16 | 0.080 | 0.02 |
| Colon | Becker | -11.39 | -19.29 | 3.33 | | | |
| | Travis (Swe/Dan) | 11.79 | -3.57 | 34.05 | | | |
| | Travis (USA) | 12.23 | -12.14 | 60.48 | | | |
| | Nekolla | 0.347 | -1.21 | 2.60 | | | |
| | *Pooled* | *4.528* | *-3.95* | *13.01* | 0.036 | 0.40 | 0.06 |
| Liver | Becker | 23.64 | 20.93 | 26.60 | | | |
| | Travis (Swe/Dan) | 9.93 | 8.40 | 11.66 | | | |
| | Travis (USA) | 3.40 | 2.08 | 5.22 | | | |
| | Dos Santos | 48.84 | 37.48 | 61.51 | | | |
| | Mori (Serie 1) | 2.49 | 1.59 | 3.86 | | | |
| | Kido | 3.25 | 1.97 | 5.20 | | | |
| | Mori (autopsy) | 0.99 | 0.85 | 1.13 | | | |
| | Nekolla | 5.41 | 1.71 | 11.38 | | | |
| | Wick 1999 | -4.39 | -7.62 | 10.92 | | | |
| | *Pooled* | *14.20* | *12.82* | *15.57* | 0.104 | 0.070 | 0.10 |
| Trachea, bronchus, lung | Becker | 0.21 | -0.09 | 0.64 | | | |
| | Travis (Swe/Dan) | 1.01 | 0.40 | 2.04 | | | |
| | Travis (USA) | 0.91 | 0.03 | 2.49 | | | |
| | Dos Santos | 0.83 | -0.48 | 3.88 | | | |
| | Mori (Serie 1) | 0.22 | -0.41 | 1.63 | | | |
| | Kido | -0.27 | -0.78 | 1.23 | | | |
| | Nekolla | -1.51 | -4.34 | 2.22 | | | |
| | Wick 2009 | -2.14 | -4.343 | 0.505 | | | |
| | Wick 2009 | -3.03 | -5.56 | 0.303 | | | |
| | *Pooled Ra (+Mori autop) included* | *-1.37* | *-2.19* | *-0.56* | 0.32 | 0.570 | -0.25 |
| | *Pooled Ra (+Mori autop) excluded* | *0.52* | *0.22* | *0.83* | | | 0.094 |

## SUPPLEMENTAL TABLE 1 cont.

| Organ/ Organsystem | Study | Excess Relative Risk per Gy | Lower CI | Upper CI | Dose $^{211}$At-mAb (Gy) | Mortality per 100 | Excess mortality per 100 |
|---|---|---|---|---|---|---|---|
| Bone and articular cartilage | Becker | 1.28 | 0.51 | 2.53 | | | |
| | Travis (USA) | 3.96 | 0.30 | 14.84 | | | |
| | Dos Santos | 2.46 | 0.66 | 6.03 | | | |
| | Nekolla | 2.83 | 2.13 | 3.68 | | | |
| | *Pooled* | *2.63* | *1.97* | *3.30* | 0.182 | 0.004 | 0.0018 |
| Breast | Nekolla | 6.97 | -1.31 | 19.70 | | | |
| | Wick | 4.14 | -30.46 | 44.55 | | | |
| | *Pooled* | *3.45* | *-10.44* | *17.34* | 0.028 | 0.373 | 0.04 |
| Urinary bladder | Nekolla | 10.1 | 1.40 | 22.70 | 0.38 | 0.076 | 0.29 |
| Kidney | Becker | 4.99 | -12.22 | 37.11 | | | |
| | Travis (Swe/Dan) | 38.38 | 9.11 | 83.56 | | | |
| | Travis (USA) | 14.82 | -21.33 | 184.22 | | | |
| | Mori (Serie 1) | -2.44 | -19.78 | 137.56 | | | |
| | Mori (Autopsy) | -1.19 | -14.44 | 23.78 | | | |
| | Nekolla | 2.00 | -0.99 | 7.30 | | | |
| | Wick 2009 | 13.22 | 2.30 | 28.92 | | | |
| | *Pooled* | *14.93* | *3.94* | *25.92* | 0.34 | 0.067 | 0.34 |
| Lymphoid hematopoietic system | Becker | 2.11 | 1.48 | 2.87 | | | |
| | Travis (Swe/Dan) | 1.88 | 1.23 | 2.69 | | | |
| | Travis (USA) | 1.91 | 0.71 | 3.60 | | | |
| | Dos Santos | 3.89 | 1.78 | 7.14 | | | |
| | Mori (Serie 1) | 3.32 | 1.26 | 6.72 | | | |
| | Kido | 3.01 | 0.48 | 8.46 | | | |
| | Mori (Autopsy) | 0.37 | 0.09 | 1.51 | | | |
| | Nekolla | 0.65 | 0.08 | 1.53 | | | |
| | Wick 2009 | 4.97 | 2.17 | 8.86 | | | |
| | *Pooled* | *2.17* | *1.68* | *2.66* | 0.03 | 0.28 | 0.02 |

* $$ERR/Gy = \frac{RR - 1}{Gy}$$

## SUPPLEMENTAL TABLE 2

Observed and expected cancer per organ and study

| Organ(s) | Study | Observed | Expected | Risk Ratio | Excess |
|---|---|---|---|---|---|
| **Lip, oral cavity, pharynx** | Becker 2008 | 8 | 2,0 | 4,00 | 6,0 |
| | Travis 2003 Swe/Dan | 5 | 4,0 | 1,25 | 1,0 |
| | Travis 2003 US | 4 | 0,7 | 5,97 | 3,3 |
| **Stomach** | Becker 2008 | 33 | 30,7 | 1,07 | 2,3 |
| | Travis 2003 Swe/Dan | 13 | 10,8 | 1,20 | 2,2 |
| | Mori series 1 1999 | 12 | 16,6 | 0,72 | -4,6 |
| | Nekolla 2010 | 18 | 13,8 | 1,30 | 4,2 |
| | Wick 1999 | 18 | 12,2 | 1,48 | 5,8 |
| | Mori 1999 autopsy | 21 | 49,0 | 0,43 | -28,0 |
| **Colon** | Becker 2008 | 6 | 11,5 | 0,52 | -5,5 |
| | Travis 2003 Swe/Dan | 16 | 10,7 | 1,50 | 5,3 |
| | Travis 2003 US | 5 | 3,3 | 1,52 | 1,7 |
| | Nekolla 2010 | 15 | 13,6 | 1,10 | 1,4 |
| **Liver, intrahepatic bile ducts** | Becker 2008 | 279 | 1,7 | 164,12 | 277,3 |
| | Travis 2003 Swe/Dan | 153 | 2,2 | 69,55 | 150,8 |
| | Travis 2003 US | 22 | 0,9 | 24,44 | 21,1 |
| | dos Santos Silva 2003 | 67 | 0,2 | 338,00 | 66,8 |
| | Mori serie 1 1999 | 79 | 4,3 | 18,24 | 74,7 |
| | Kido serie 2 1999 | 64 | 2,7 | 23,45 | 61,3 |
| | Nekolla 2010 | 10 | 2,4 | 4,17 | 7,6 |
| | Wick1999 | 1 | 2,3 | 0,43 | -1,3 |
| | Mori 1999 autopsy | 263 | 33,7 | 7,80 | 229,3 |
| **Trachea, broncus, lung** | Becker 2008 | 48 | 38,9 | 1,23 | 9,1 |
| | Travis 2003 Swe/Dan | 28 | 13,3 | 2,11 | 14,7 |
| | Travis 2003 US | 12 | 6,0 | 2,00 | 6,0 |
| | dos Santos Silva 2003 | 4 | 2,1 | 1,90 | 1,9 |
| | Mori series 1 1999 | 8 | 6,4 | 1,24 | 1,6 |
| | Kido series 2 1999 | 3 | 4,3 | 0,70 | -1,3 |
| | *Nekolla 2010* | *29* | *34,1* | *0,85* | *-5,1* |
| | *Wick 2009* | *45* | *57,1* | *0,79* | *-12,1* |
| | *Wick1999* | *25* | *35,7* | *0,70* | *-10,7* |
| | *Mori 1999 autopsy* | *16* | *53,3* | *0,31* | *-37,3* |
| **Bone and articular cartilage** | Becker 2008 | 10 | 1,4 | 7,14 | 8,6 |
| | Travis 2003 US | 2 | 0,1 | 20,00 | 1,9 |
| | dos Santos Silva 2003 | 5 | 0,4 | 12,82 | 4,6 |
| | Nekolla 2010 | 57 | 1,0 | 57,00 | 56,0 |
| **Breast** | *Becker 2008* | *9* | *6,4* | *1,41* | *2,6* |
| | *Travis 2003 Swe/Dan* | *27* | *15,9* | *1,70* | *11,1* |
| | *Travis 2003 US* | *6* | *2,9* | *2,07* | *3,1* |
| | *dos Santos Silva 2003* | *3* | *1,4* | *2,22* | *1,7* |
| | Nekolla 2010 | 12 | 7,1 | 1,69 | 4,9 |
| | Wick 2009 | 6 | 6,6 | 0,91 | -0,6 |

| Organ(s) | Study | Observed | Expected | Risk Ratio | Excess |
|---|---|---|---|---|---|
| **Urinary bladder** | *Becker 2008* | *7* | *5,7* | *1,23* | *1,3* |
| | *Travis 2003 Swe/Dan* | *8* | *6,7* | *1,19* | *1,3* |
| | *Travis 2003 US* | *3* | *0,8* | *3,75* | *2,2* |
| | Nekolla 2010 | 16 | 8,0 | 2,00 | 8,0 |
| **Kidney** | Becker 2008 | 6 | 4,9 | 1,22 | 1,1 |
| | Travis 2003 Swe/Dan | 12 | 4,4 | 2,73 | 7,6 |
| | Travis 2003 US | 1 | 0,6 | 1,67 | 0,4 |
| | Mori serie 1 1999 | 1 | 1,1 | 0,88 | -0,1 |
| | Nekolla 2010 | 7 | 4,2 | 1,67 | 2,8 |
| | Wick 2009 | 18 | 9,1 | 1,98 | 8,9 |
| | Mori 1999 autopsy | 6 | 6,3 | 0,95 | -0,3 |
| **Lymphoid, hematopoietic and related tissues** | Becker 2008 | 57 | 10,5 | 5,43 | 46,5 |
| | Travis 2003 Swe/Dan | 44 | 8,9 | 4,94 | 35,1 |
| | Travis 2003 US | 13 | 2,6 | 5,00 | 10,4 |
| | dos Santos Silva 2003 | 12 | 1,3 | 9,16 | 10,7 |
| | Mori serie 1 1999 | 9 | 1,1 | 7,96 | 7,9 |
| | Kido serie 2 1999 | 4 | 0,5 | 7,33 | 3,5 |
| | Nekolla 2010 | 12 | 5,4 | 2,22 | 6,6 |
| | Wick 2009 | 21 | 6,8 | 3,09 | 14,2 |
| | Mori 1999 autopsy | 29 | 16,4 | 1,77 | 12,6 |
| | Total number (all studies) | 1753 | | | |

Studies marked in Italic contain risk ratio data but are not used due to lacking organ dose data or exposure group is questionable as discussed in main article.

## SUPPLEMENTAL TABLE 3

Weighting factors per age group

| **Age (years)** | Deceased, N | Total individuals at risk, N | $w_i$ fraction of total population |
|---|---|---|---|
| **65-69** | 24944 | 409628 | 0,970 |
| **70-74** | 31922 | 381195 | 0,903 |
| **75-79** | 45675 | 342397 | 0,811 |
| **80-84** | 74076 | 282521 | 0,669 |
| **85+** | 245483 | 122742 | 0,291 |

Based on the assumption of a constant death rate.
N, numbers

Mortality data (females aged 65-85+), from Statistics Sweden:

Official Statistics of Sweden: Deaths by region, age (during the year) and sex. 2007-2016. https://www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101I/DodaHandelseK/ accessed on 03.12.2020.

## SUPPLEMENTAL TABLE 4 *

| | $^{211}$At dose mGy | Male and female derived ERR/Gy | | Female sex only derived ERR/Gy | | 2nd CA risk following Ovarian CA primary | | Low LET = high LET Age Adjustment |
|---|---|---|---|---|---|---|---|---|
| | | **ERR/Gy** (95% CI) | *Excess | **ERR/Gy** (95% CI) | *Excess | **HR** (95% CI) | *Excess | *Excess |
| Lip, oral cavity, pharynx | 280 | 15.2 (2.7 - 28) | 0.157 | 51.7 (**1.2 - 202**) | 0.535 | 0.96 (0.59-1.56) | 0.151 | *0.157* |
| Stomach | 160 | 1.4 (-5.0 - 7.9) | 0.018 | 10.3 (-10 - 45) | 0.132 | 1.64 (0.99-2.74) | 0.030 | *0.018* |
| Colo-rectum, anal | 36 | 4.5 (-3.5 - 13) | 0.065 | -9.0 (-22 - 30) | -0.128 | 1.03 (0.87-1.22) | 0.067 | *0.065* |
| Liver, intrahepatic bile ducts | 104 | 14.2 (13 - 16) | 0.103 | 19.2 (13 - 25) | 0.139 | 3.56 (1.83-6.93) | 0.367 | *0.103* |
| Trachea, bronchus, lung | 320 | 0.52 (0.21 - 0.82) | 0.094 | 2.0 (0.1 - 5.4) | 0.360 | 1.06 (0.73-1.53) | 0.100 | *0.094* |
| Bone and artic. cartilage | 182 | 2.6 (2.0 - 3.3) | 0.002 | 1.9 (0.7 - 3.8) | 0.001 | 1.40 (0.70-2.82) | 0.0028 | 0.001 |
| Breast (female) | 28 | 3.45 (-10 - 17) | 0.036 | 3.45 (-10 – 17) | *0.036* | 1.12 (1.01-1.23) | 0.040 | 0.018 |
| Kidney | 340 | 14.9 (3.9 - 26) | 0.342 | 9.6 (-7.5 - 27) | 0.220 | 0.82 (0.44-1.5) | 0.280 | *0.342* |
| Urinary bladder | 380 | 10.1 (1.4 - 23) | 0.292 | | 0.292 † | 1.63 (1.05-2.51) | 0.476 | *0.292* |
| Lymphoid, haem-opoetic | 30 | 2.17 (1.7 - 2.7) | 0.018 | 1.9 (0.7 - 3.8) | 0.016 | 1.11 (0.67-1.82) | 0.020 | *0.018* |
| **Total Excess mortality per 100 treated** | | | **1.13** | | **1.60** | | **1.53** | **1.11** |

**SUPPLEMENTAL Table 4**. Various assumptions or used background with its impact on Excess relative risk per Gray (ERR/Gy) and on Excess mortality per 100 treated. * Excess data is here calculated for a standard patient of 55 years of age at time of treatment.

The larger 95% CI for 'Female only' is due to fewer events (145 observed / 56.7 expected), out of which 63 / 40.3 (Obs/Exp) concerned breast cancer, while 'Male and female derived ERR/Gy' are based on totally 1757 / 572 (Obs/Exp), as seen in Table 1 and 2 and specified in Supplemental Table 2.

The low LET = high LET assumption 'Excess' figures in *Italic* are identical with the data in column 'Male and female derived ERR/Gy', as this age adjustment only concerns the figures for 'Breast' and 'Bone and articulate cartilage'.

Hazard Ratio (column 7) for a new primary cancer following a first ovarian cancer diagnosis. Data per organ from *(Nielsen et al. CMAJ 2012. DOI:10.1503/cmaj.110167)*, were multiplied with the Excess cancer presented in column 4, to give a new number of 'Excess cancer / 100 treated' presented in column 8. No adjustment for any accompanying decreased survival due to the second primary cancer is performed.

† No dose data was available for urinary bladder where excessive risk data exist, therefore the total Excess data from 'Male and female' is used also in 'Female sex only'.

CI, confidence interval. LET, linear energy transfer. CA, cancer. HR, Hazard ratio.

## SUPPLEMENTAL TABLE 5

Excess cancer cases per 100 treated according to Age, at time of treatment

| | 25 year | | 35 year | | 45 year | | 55 year | | 65 year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M&F | F | M&F | F | M&F | F | M&F | F | M&F | F |
| Lip, oral cavity, pharynx | 0.192 | 0.654 | 0.191 | 0.650 | 0.178 | 0.607 | 0.157 | 0.535 | 0.115 | 0.391 |
| Stomach | 0.021 | 0.152 | 0.021 | 0.150 | 0.019 | 0.141 | 0.018 | 0.132 | 0.014 | 0.105 |
| Colo-rectum, anal | 0.071 | -0.139 | 0.070 | -0.139 | 0.067 | -0.133 | 0.065 | -0.128 | 0.053 | -0.105 |
| Liver, intrahepatic bile ducts | 0.113 | 0.153 | 0.113 | 0.153 | 0.108 | 0.147 | 0.103 | 0.139 | 0.082 | 0.110 |
| Trachea, bronchus, lung | 0.111 | 0.422 | 0.111 | 0.424 | 0.106 | 0.404 | 0.094 | 0.360 | 0.061 | 0.234 |
| Bone and artic. cartilage | 0.002 | 0.002 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 | 0.001 | 0.001 |
| Breast (female) | 0.047 | 0.047 | 0.046 | 0.046 | 0.042 | 0.042 | 0.036 | 0.036 | 0.026 | 0.026 |
| Kidney | 0.364 | 0.234 | 0.365 | 0.235 | 0.353 | 0.227 | 0.342 | 0.220 | 0.279 | 0.180 |
| Urinary bladder | 0.298 | 0.298 | 0.299 | 0.299 | 0.292 | 0.292 | 0.292 | 0.292 | 0.253 | 0.253 |
| Lymphoid, haemopoetic | 0.019 | 0.017 | 0.019 | 0.017 | 0.019 | 0.016 | 0.018 | 0.016 | 0.015 | 0.014 |
| Male and female | **1.24** | | **1.24** | | **1.19** | | **1.13** | | **0.90** | |
| Female only | | **1.84** | | **1.84** | | **1.74** | | **1.60** | | **1.21** |

Excess cancer cases per 100 treated depending on various age at time of treatment. Data presented as Male and female' or 'Female only' using the ERR/Gy as presented in Supplemental Table 4.

M&F, 'Male and Female' derived background data of observed/expected to calculate the ERR/Gy.

F, 'Female only' derived background data of observed/expected to calculate the ERR/Gy.