Review

Ionising radiation as a risk factor for lymphoma: a review

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Abstract

The ability of ionising radiation to induce lymphoma is unclear. Here, we present a narrative review of epidemiological evidence of the risk of lymphoma, including chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), among various exposed populations including atomic bombing survivors, industrial and medical radiation workers, and individuals exposed for medical purposes. Overall, there is a suggestion of a positive dose-dependent association between radiation exposure and lymphoma. The magnitude of this association is highly imprecise, however, with wide confidence intervals frequently including zero risk. External comparisons tend to show similar incidence and mortality rates to the general population. Currently, there is insufficient information on the impact of age at exposure, high versus low linear energy transfer radiation, external versus internal or acute versus chronic exposures. Associations are stronger for males than females, and stronger for non-Hodgkin lymphoma and MM than for Hodgkin lymphoma, while the risk of radiation-induced CLL may be non-existent. This broad grouping of diverse diseases could potentially obscure stronger associations for certain subtypes, each with a different cell of origin. Additionally, the classification of

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malignancies as leukaemia or lymphoma may result in similar diseases being analy"ed separately, while distinct diseases are analy"ed in the same category. Uncertainty in cell of origin means the appropriate organ for dose response analy"sis is unclear. Further uncertainties arise from potential confounding or bias due to infectious causes and immunosuppression. The potential interaction between radiation and other risk factors is unknown. Combined, these uncertainties make lymphoma perhaps the most challenging malignancy to study in radiation epidemiology.

Keywords: lymphoma, multiple myeloma, chronic lymphocytic leukaemia, ionising radiation

(Some figures may appear in colour only in the online journal)

1. Introduction

Lymphomas comprise a diverse group of malignancies involving cells of the immune system. These diseases include (1) precursor cell lymphoid malignancies involving proliferation of immature lymphoblasts, and (2) mature lymphoid malignancies involving differentiated B- and T-cells (figure 1, table 1) [1, 2]. Lymphomas are classed as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) according to the presence or absence of Reed-Sternberg cells, respectively [3, 4]. Lymphoma belongs to the wider disease category of lymphoid malignancies. These diseases may present as leukaemia, with proliferation predominantly occurring in the bone marrow and blood, or as lymphoma, in which proliferating cells form extra-marrow mass lesions. Solid tumours are typically found in lymph nodes, though can occur anywhere in the body where lymphoid tissue is found (e.g. [5, 6]). The distinction between leukaemia and lymphoma is now regarded as artificial [7, 8], as these malignancies have considerable histological overlap, with many diseases involving both solid and circulating phases [9]. For example, chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are considered to be histologically the same disease [10], with the former involving proliferation in the blood and marrow, and the latter forming solid tumours. These two disease manifestations are given separate International Classification of Diseases (ICD) and ICD Oncology (ICD-O) [11, 12] codes, however. Likewise, acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) are regarded as a single disease entity [1], though are coded differently. Multiple myeloma (MM) and hairy cell leukaemia (HCL) are malignancies of mature B-lymphocytes, and thus are considered sub-types of NHL [1], though again they have distinct ICD and ICD-O codes and are almost invariably analysed separately in epidemiological studies and recorded as separate disease entities in cancer statistics (e.g. [13]).

1.1. Epidemiology

Around 120 000 cases of HL and NHL, including MM and CLL, are diagnosed each year in the USA [14], while around 25 000 cases are diagnosed in the UK, representing around 7% of total cancer cases [15–18]. Overall, incidence of NHL exceeds HL by a factor of around ten [3, 4], though between the ages of 10 and 30 years, HL tends to be the more common form, especially in Europe and North America [13]. In teenagers, lymphomas represent around a quarter of all cancers. All major mature lymphoid malignancy subtypes are more common in males [15–18]. Both CLL and MM are extremely rare before age 50 years and almost unknown in childhood [19, 20].
1.2. Non-radiogenic risk factors

Most forms of both HL and NHL are strongly associated with congenital, acquired or drug-induced immunosuppression [21, 22]. Greatly elevated rates have been observed among individuals with HIV/AIDS and those receiving immunsuppressant drugs following organ transplantation [21]. Certain infections are also associated with lymphoma, including Epstein–Barr virus [23], hepatitis C virus [24] and Helicobacter pylori [4]. Positive associations have been found between autoimmune conditions and several lymphoma subtypes [24]. Smoking has also been identified as a risk factor, especially for T-cell NHL and HL [25, 26]. Obesity may be associated with increased risk of large B-cell NHL [27], though not CLL/SLL [28]. Alcohol consumption is associated with reduced rates of both NHL [22, 29] and HL [30], while there is a possible negative association between HL and ultraviolet radiation exposure [31]. Elevated lymphoma rates have been observed in certain occupational groups, including crop farmers, painters, textile workers and women’s hairdressers [32], suggesting that certain chemicals may be a risk factor [33]. There is no evidence of any impact of socio-economic status on risk of MM or CLL [34]. There is a suggestion of increased HL incidence for most deprived areas, but for males only [34].

1.3. Cellular origins of lymphoma

While most lymphomas are formed of mature lymphocytes, these cells do not necessarily represent the origin of the disease. Alternatives include lymphoblasts, multi-lymphoid progenitor...
Table 1. Interlymph classification [1] of lymphoid malignancies. The ‘grouping’ column represents the disease each malignancy is usually categorised as in epidemiological studies, e.g. follicular lymphoma is included within the category ‘NHL’ or the broader category of all lymphomas. Diseases in bold are the subject of this review.

| Disease category          | Study grouping                  |
|--------------------------|---------------------------------|
| **Lymphoid malignancies**|                                 |
| Hodgkin lymphoma         | Classic Hodgkin lymphoma, nodular sclerosing (HL, lymphoma) |
| Precursor cell           | Acute lymphoblastic leukaemia/lymphoblastic lymphoma (ALL/NHL, lymphoma) |
| **Non-Hodgkin lymphomas**|                                 |
| Mature lymphocytes       | Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/NHL, lymphoma) |
| B-cell                   | Multiple myeloma (MM)           |
|                          | Haemat cell leukaemia (HCL, leukaemia) |
|                          | Mantle cell lymphoma (NHL, lymphoma) |
|                          | Diffuse Large B-cell lymphoma (NHL, lymphoma) |
|                          | Follicular lymphoma (NHL, lymphoma) |
| T- and NK-cell           | NK/T-cell lymphoma (NHL, lymphoma) |
cells and haematopoietic stem cells (figure 1) [35, 36]. Each cell type may be found in different locations, including the bone marrow, blood, spleen, thymus or germinal centres in lymph nodes, according to stage of lymphopoiesis. T-lymphocytes, for example, initially develop in the marrow before being released into the blood, maturing in the thymus, then migrating to a lymph node or other lymph tissue. One or more radiation-induced genetic mutations may occur at any of these stages and locations, while the tumour itself may develop somewhere else. Evidence is emerging that at least some lymphomas develop from ‘lymphoma stem cells’ residing in the marrow [35]. Cases have been reported of allogenic bone marrow transplant donors and recipients both developing identical mature lymphoid malignancies, often at the same time, post-transplant [35]. Further evidence comes from cases of ‘composite lymphomas’, in which the patient develops multiple, histologically distinct lymphomas, derived from a common precursor cell [37].

This uncertainty in the cell of origin for lymphoma is almost unique in radiation epidemiology, where the site of a tumour is generally assumed to be the site of cell proliferation and the site of initial and subsequent genetic mutations, thus defining the tissue/organ for which dose must be estimated in dose response analysis. Consequently, there is no consensus on the appropriate target organ for lymphoma. Most epidemiological dose response analyses for lymphoma are based on bone marrow dose, although colon dose [38], personal dosimeter reading (in occupational studies) and mean lymphocyte dose [39] have also been used. An additional exposure pathway for circulating lymphocytes, relevant to inhaled alpha-emitting radionuclides such as radon, is via the transbronchial epithelium in the lungs [40]. While often similar, mean lymphocyte and bone marrow doses may differ by a factor of up to 2.6, depending on exposed region [41]. Along with potential misclassification and the profound impact of immunosuppression, the uncertainty in cellular origin complicates assessment of the relationship between radiation and lymphoma. The findings of the epidemiological studies discussed in the remainder of this review should be placed in the context of this uncertainty.

2. Epidemiological evidence of ionising radiation as a risk factor for lymphoma

We searched PubMed for English language epidemiological studies (cohort and case control) analysing lymphoma risks following radiation exposure. We searched using the MeSH terms ‘Lymphoma’ and the respective MeSH terms for each sub-type of lymphoma including broad categories ‘Non-Hodgkin lymphoma’ and ‘Hodgkin lymphoma’, and the MeSH terms for ionising radiation, background radiation, x-rays, gamma rays and alpha and beta radiation. This search yielded 3156 items, of which 106 were selected. The reference lists of included papers and previous reviews of lymphoma risks [42, 43] were also searched. No restriction was applied for publication period. As external analyses may be potentially biased, e.g. due to healthy worker effect, a greater weight was given to those publications reporting a dose response based on internal analysis.

As mentioned in the introduction, CLL and MM are regarded as subtypes of NHL [1], but are almost always analysed separately and will be reported as described in the cited papers. We assumed that papers reporting figures for ‘lymphoma’ without giving further details were restricted to the current (3rd edition, 1st revision) ICD-O-3 codes [12] 9590 to 9729. ‘Hodgkin lymphoma’ was restricted to codes 9650 to 9667 and ‘non-Hodgkin lymphoma’ implied codes 9670–9729 (thus not including CLL, MM or HCL). Dose units are written as reported in the cited papers. An equivalent dose of 1 sievert (Sv) corresponds to a dose of 1 gray (Gy), averaged over the whole organ, for photons and electrons. Where there is a neutron or alpha component, this equivalency no longer applies.
2.1. Atomic bombing survivors

The Life Span Study (LSS) of atomic bombing survivors includes around 94,000 residents of Hiroshima and Nagasaki [44–46] who received reasonably uniform external whole-body exposures of low linear energy transfer (LET) gamma and high LET neutron radiation, at an extremely high dose rate. A summary of findings is presented in table 2. As of 2003, there were 284 deaths from lymphoma in the LSS. In the latest mortality analysis [45], based on bone marrow dose, the excess relative risk (ERR) was 0.16 Gy\(^{-1}\) (95% CI: −0.13, 0.59), compared to 0.47 Gy\(^{-1}\) (95% CI: 0.38, 0.56) for all solid cancers and 3.1 Gy\(^{-1}\) (95% CI: 1.8, 4.3) for leukaemia. No separate analysis was performed by lymphoma subtype. A raised lymphoma ERR was found for males (0.70 Gy\(^{-1}\), 95% CI: 0.08–1.70), but not for females (−0.18, 95% CI: −0.21–0.24). Likewise for the incidence analysis [46], a suggestion of a raised ERR was observed for males for NHL (0.46 Gy\(^{-1}\), 95% CI: −0.08, 1.29) but not females (0.02 Gy\(^{-1}\), 95% CI: −0.44, 0.64). There is some overlap in the confidence intervals for the male and female ERR figures, suggesting the apparent sex differences may be a chance finding. The ERR for HL was 0.20 Gy\(^{-1}\) (95% CI: −1.03, 2.63), based on 35 incident cases. A significant linear dose response was reported for CLL, based on 10 cases, plus two cases of HCL. No quantification other than a p-value (<0.05) was reported, however. For MM, there is a somewhat stronger dose response for the mortality data (0.54 Gy\(^{-1}\), 95% CI: −0.04, 1.58) than for incidence (0.38 Gy\(^{-1}\), 95% CI: −0.23, 1.36).

In a detailed analysis of lymphoma mortality among male atomic bombing survivors aged 15–64 years at the time of exposure, Richardson et al [38] reported positive associations for the periods 35–45 years (ERR = 2.23 Sv\(^{-1}\), 90% CI: 0.09, 6.91) and 46–55 years (1.70, 95% CI: 0.16, 5.36) since exposure, but not for 5–25 years (0.08) and 26–35 years (−0.10). Confidence intervals were undefined in both cases. A similar, but stronger, pattern was observed for NHL alone. The authors also reported a higher ERR when analysis was restricted to survivors receiving doses below 0.5 Sv, compared to the whole dose range. Although this suggests non-linearity of dose response, the introduction of a quadratic term did little to improve goodness of fit, compared to a purely linear model [38].

2.2. Occupational exposures

Most studies of occupational exposures have focussed on individuals working in the nuclear industry (including uranium workers [47–62] and Chernobyl clean-up workers [7, 63, 64]), nuclear weapons testing programs [65–71], medical imaging [56, 72–78] or those working as airline crew [79–84]. Radiation exposures are typically fairly uniform, though highly protracted. The potential impact of ‘healthy worker’ effects should be considered when interpreting external comparisons of cancer incidence or mortality. In many occupational studies (e.g. [84, 85]), rates for all cancer types are decreased, compared to the general population, even those normally strongly associated with radiation. A greater weight should therefore be placed on the results of studies including internal analysis with a dose response. A summary of standardised incidence ratios (SIR), standardised mortality ratios (SMR) and relative risks (RRs) for studies with >20 cases is presented in table 3, while table 4 shows a summary of ERR figures.

The most informative studies are those of large pooled cohorts of nuclear workers [87–99], which include dose response analyses based on estimated bone marrow dose from external sources, derived from personal dosimeters. The recent study by Leuraud et al [94] involved a France-UK-USA cohort called INWORKS. Although the sample size was smaller than the previous 15-country nuclear workers study [98] (302 297 versus 407 391), the increased follow-up of the INWORKS cohort yielded a much larger number of deaths, including 710 from NHL,
Table 2. Excess relative risk (ERR) from the life span study (LSS) of Japanese atomic bombing survivors.

| Study (year) | Disease | Grouping | Sample size | Observed Incidence or Mortality | Incidence or Mortality ERR (per Gy) [95% CI] | Dose site | Lag |
|--------------|---------|----------|-------------|---------------------------------|-----------------------------------------------|-----------|-----|
| Richardson [38] (2009) | All lymphoma | Males aged 15–64 years at exposure | 20,940 | 90 | 0.79 [0.10, 1.88]\(^a\) | Colon (DS02) | 5 years\(^b\) |
| | NHL | | | | 0.86 [0.13, 2.03]\(^a\) | | 10 years |
| | | | | | 1.12 [0.26, 2.51]\(^a\) | | 5 years\(^b\) |
| | | | | | | | 10 years |
| Ozasa [45] (2012) | All lymphoma | All | 86,611 | 284 | 0.16 [−0.13, 0.59] | Bone marrow (DS02) | 5 years\(^b\) |
| | | Male | 125 | 0.70 [0.08, 1.70] | | |
| | | Female | 159 | −0.18 [−0.21, 0.24] | | |
| | | MM | 93 | 0.54 [−0.04, 1.58] | | |
| | | Male | 34 | 0.11 [NA, 1.6] | | |
| | | Female | 59 | 0.86 [0.02, 2.50] | | |
| | MM All | 35 | 0.20 [−1.03, 2.63] | | |
| Hsu [46] (2013) | NHL | Male | 113,011\(^c\) | 402 | 0.46 [−0.08, 1.29] | Bone marrow (DS02) | 5 years\(^b\) |
| | | Female | | | 0.02 [−0.44, 0.64] | |
| | HL | All | 35 | 0.20 [−1.03, 2.63] | | |
| | MM | All | 136 | 0.38 [−0.23, 1.36] | | |

\(^a\) 90% confidence interval.
\(^b\) The 5-year lag period is implicit as the study only began accruing cases in 1950.
\(^c\) Includes 'not in city' group. DS02 = 2002 version of dosimetry system.
Table 3. Summary of standardised incidence ratio (SIR), standardised mortality ratio (SMR) and relative risk (RR) for occupational exposures.

| Study (year) | Disease | Grouping | Sample size (exposed/unexposed) | Observed cases/ deaths | SIR/SMR [95% CI] |
|--------------|---------|----------|---------------------------------|------------------------|------------------|
| Darby [86] (1995) Underground miners | NHL | <10 YSE | 64,209 | 6 | 0.81 [0.30–1.77] |
| | All | >10 YSE | 30 | 0.79 [0.54–1.13] |
| | All | | 36 | 0.80 [0.56–1.10] |
| | HL | <10 YSE | 5 | 0.77 [0.25–1.80] |
| | All | >10 YSE | 12 | 1.01 [0.52–1.77] |
| | All | | 17 | 0.93 [0.54–1.48] |
| Mohan [74] (2003) Medical radiographers | MM | Female | 146,022 | 80 | 1.01 [0.7, 1.6] |
| | All | Male | 133 | 0.98 [0.7, 1.1] |
| | HL | Male | 9 | 0.61 [0.3, 1.2] |
| | Female | 25 | 1.06 [0.7, 1.6] |
| | MM | Female | 33 | 0.91 [0.6, 1.3] |
| Sigurdson [75] (2003) US Radiographers | NHL | Female | 69,524 | 88 | 1.21 [0.95, 1.48] |
| | All | Male | 20,781 | 47 | 1.03 [0.74, 1.40] |
| | All | 90,305 | 135 | 1.14 [0.95, 1.34] |
| | HL | Female | 69,524 | 21 | 1.28 [0.79, 1.96] |
| | All | Male | 20,781 | 11 | 1.69 [0.83, 3.06] |
| | All | 90,305 | 32 | 1.40 [0.96, 1.98] |
| | MM | Female | 69,524 | 16 | 0.90 [0.49, 1.52] |
| | All | Male | 20,781 | 10 | 0.89 [0.39, 1.73] |
| | All | 90,305 | 26 | 0.90 [0.57, 1.36] |
| | CLL | Female | 69,524 | 14 | 1.25 [0.58, 2.35] |
| | All | Male | 20,781 | 10 | 1.10 [0.50, 2.09] |
| | All | 90,305 | 24 | 1.18 [0.72, 1.83] |
Table 3. (continued)

| Study (year)                      | Disease | Grouping                          | Sample size (exposed/un-exposed) | Observed cases/deaths | SIR/SMR [95% CI] |
|----------------------------------|---------|-----------------------------------|----------------------------------|-----------------------|------------------|
| Gun [69] (2008) Nuclear weapons test participants | MM      | Whole cohort (79% received doses of <1 mSv) | 10983                          | 29, 21                | 1.22 [0.82, 1.75], 1.19 [0.74, 1.82] |
| Muirhead [87] (2009) UK Radiation workers | NHL     | Whole cohort                       | 174 541                         | 206                   | 0.93 [0.80, 1.06] |
|                                  | HL      | (90% male)                         |                                  | 28                    | 0.81 [0.54, 1.17] |
|                                  | MM      |                                   |                                  | 97                    | 0.83 [0.67, 1.01] |
| Boice [88] (2011) Rocketdyne nuclear workers | HL      | Any ext. radiation                 | 5743                            | 5                     | 1.64 [0.53, 3.83] |
|                                  |        | Any int. radiation                 | 2232                            | 2                     | 1.60 [0.19, 5.76] |
|                                  |        | Total                              | 5801                            | 5                     | 1.63 [0.53, 3.79] |
|                                  | NHL     | Any ext. radiation                 | 5743                            | 31                    | 1.01 [0.69, 1.44] |
|                                  |        | Any int. radiation                 | 2232                            | 11                    | 0.92 [0.46, 1.64] |
|                                  |        | Total                              | 5801                            | 31                    | 1.00 [0.68, 1.43] |
|                                  | MM      | Any ext. radiation                 | 5743                            | 10                    | 0.71 [0.34, 1.30] |
|                                  |        | Any int. radiation                 | 2232                            | 5                     | 0.92 [0.30, 2.14] |
|                                  |        | Total                              | 5801                            | 10                    | 0.71 [0.34, 1.30] |
|                                  | CLL     | Any ext. radiation                 | 5743                            | 8                     | 1.36 [0.59, 2.68] |
|                                  |        | Any int. radiation                 | 2232                            | 4                     | 1.76 [0.48, 4.51] |
|                                  |        | Total                              | 5801                            | 8                     | 1.35 [0.58, 2.66] |
| Silver [58] (2013) Male uranium workers | NHL     | Salaried                           | 3633                            | 18                    | 0.97 [0.58, 1.54] |
|                                  |        | Paid hourly                        | 1818                            | 12                    | 1.33 [0.69, 2.32] |
|                                  | HL      | Salaried                           | 3633                            | 5                     | 1.81 [0.59, 4.22] |
|                                  |        | Paid hourly                        | 1818                            | 1                     | 0.76 [0.02, 4.23] |
|                                  | MM      | Salaried                           | 3633                            | 12                    | 1.44 [0.75, 2.52] |
|                                  |        | Paid hourly                        | 1818                            | 7                     | 1.82 [0.73, 3.75] |
| Yong [82] (2014) US airline crew | HL      | Whole cohort                       | 5964                            | 2                     | 0.56 [0.07–2.03]  |
|                                  | NHL     | (99.9% male)                       | 964                             | 27                    | 0.75 [0.49–1.09]  |
|                                  | CLL     |                                   |                                  | 9                     | 1.14 [0.52, 2.15] |
| Study (year) | Disease | Grouping | Sample size (exposed/un-exposed) | Observed cases/deaths | SIR/SMR [95% CI] |
|-------------|---------|----------|----------------------------------|-----------------------|------------------|
| Hammer [83] (2014) Airline crew | All lymphoma | Male cockpit | 34.73b | 0.66 [0.43–0.98] |
| | | Male cabin | 28.8b | 2.04 [1.14–3.17] |
| | | Female cabin | 20.28b | 0.74 [0.41–1.25] |
| | NHL | Male cockpit | 29.47b | 0.66 [0.41–1.01] |
| | | Male cabin | 26.67b | 2.37 [1.41–3.73] |
| | | Female cabin | 13.87b | 0.64 [0.30–1.18] |
| | HL | Male cockpit | 5.26b | 0.67 [0.18–1.72] |
| | | Male cabin | 2.13b | — |
| | | Female cabin | 6.40b | 1.17 [0.36–2.91] |
| | CLL | Male cockpit | 6.32b | 0.71 [0.22, 1.71] |
| | | Male cabin | 1.07b | — |
| | | Female cabin | 1.07b | — |
| Zablotska [60] (2014) Eldorado uranium miners | HL | Male only | 14, 7 | 0.93 [0.51, 1.57], 0.76 [0.30, 1.56] |
| | NHL | Male only | 16,236 (mortality cohort), 15,366 (incidence cohort) | 80, 42 | 0.89 [0.70, 1.11], 0.91 [0.65, 1.23] |
| | MM | Male only | 20, 18 | 0.65 [0.40, 1.01], 0.81 [0.48, 1.29] |
| Zablotska [89] (2014) Canadian nuclear workers | NHL | Revised cohort (83.2% male) | 45,316 | 17 | 0.66 [0.38, 1.06] |
| Boice [90] (2014) Mound nuclear workers | HL | Workers exposed to radiation | 4977 | 3 | 0.84 [0.17, 2.45] |
| | NHL | Workers exposed to radiation | 34 | 1.14 [0.78, 1.62] |
| | MM | Workers exposed to radiation | 15 | 1.20 [0.67, 1.97] |
| Rage [51] (2018) French uranium miners | LH | Male only | 5400 | 23 | 1.02 [0.64, 1.53] |
| | MM | Male only | 5 | 0.76 [0.25, 1.78] |
| Study (year) | Disease | Grouping | Sample size (exposed/un-exposed) | Observed cases/deaths | SIR/SMR [95% CI] |
|-------------|---------|----------|----------------------------------|-----------------------|------------------|
| **Yin [91] (2017) uranium enrichment workers** | NHL | Oak Ridge, Portsmouth and Paducah sites. | 29303 | 163 | 1.06 [0.90, 1.23] |
| | MM | | | 69 | 0.98 [0.77, 1.24] |
| **Golden (2019) [173] Mallinckrodt workers** | NHL | | | 25 | 1.34 [0.87, 1.98] |
| | HL | | | 2 | 0.78 [0.09, 2.81] |
| | MM | | | 6 | 0.71 [0.26, 1.54] |
| | CLL | | | 5 | 1.07 [0.35, 2.50] |
| **Boice [71] (2020) Nuclear weapons test participants** | NHL | Whole cohort (90.2% male) | 114270 | 727 | 0.91 [0.84, 0.98] |
| | HM | | | 84 | 0.77 [0.61, 0.95] |
| | MM | | | 350 | 0.98 [0.88, 1.09] |
| | CLL | | | 159 | 0.87 [0.74, 1.01] |

* Adjusted for missing cause of death.
† Exclusion of workers monitored <1956 and addition of zero dose records.
‡ LH: Lymphatic and haematopoietic malignancies (ICD codes C81-85, C90 and C96), excluding leukaemia and other T/NK lymphoma (C86). FU: follow-up. YSE: years since beginning of employment.
Table 4. Summary of excess relative risk (ERR) for occupational studies.

| Study (year) | Disease | Grouping | Sample size (exposed/unexposed) | Observed Incidence or Mortality | ERR per Gy or Sv for Incidence or Mortality [95% CI] | Dose site | Lag period |
|--------------|---------|----------|---------------------------------|---------------------------------|------------------------------------------------------|----------|-----------|
| Kesminiene [7] (2008) Chernobyl cleanup workers | NHL | Whole cohort | 1883 | 20 | 2.81 at 0.1 Gy [0.09, 24.3] | ABM | Variable<sup>b</sup> |
| | | | | | 0.47 at 0.1 Gy [ND, 7.61]<sup>a</sup> | | |
| Richardson [38] (2009) Male Savannah River nuclear workers | All NHL lymphoma NHL | 5-year lag 10-year lag 5-year lag 10-year lag | 1883 | 56 | 6.99 [0.96, 18.39]<sup>a</sup> | Whole body | 5 years |
| | | | | | 8.18 [1.44, 21.16]<sup>a</sup> | | |
| | | | | | 6.45 [0.48, 17.95]<sup>a</sup> | | |
| | | | | | 7.62 [0.93, 20.77]<sup>a</sup> | | |
| Akiba [93] (2012) Japanese nuclear workers | NHL MM | Whole cohort (male only) | 200583 | 51 | 2.72 [−5.58, 23.13] | Unclear | 10 years |
| | | | | | 13.96 [−1.59, 57.8] | | |
| Zablotska [63] (2013) Chernobyl cleanup workers | CLL | Whole cohort (male only) | 110645 | 65 | 2.58 (0.02; 8.43) | ABM | 2 years |
| Zablotska [60] (2014) Eldorado uranium miners | HL NHL MM | Whole cohort (male only) | 201485 | 10/7 | 13.0 [<0, 139], −0.29 [ND] | Whole body | 5 years |
| | | | | | −0.34 [ND], 3.54 [−0.29, 29.5] | | |
| | | | | | −0.34 [ND], −0.29 [ND] | | |
| Leuraud [94] (2015) INWORKS nuclear workers | NHL HL MM CLL | Whole cohort (87% male) | 308297 | 710 | 0.47–0.76, 2.03 | ABM | 10 years |
| | | | | | 2.94 [ND, 11.49]<sup>a</sup> | | |
| | | | | | 0.84 [−0.96, 3.33]<sup>a</sup> | | |
| | | | | | −1.06 [ND, 1.81]<sup>a</sup> | | |
| Study (year)                        | Disease Grouping                              | Sample size (exposed/unexposed) | Observed Incidence or Mortality | ERR per Gy or Sv for Incidence or Mortality [95% CI] | Dose site | Lag period |
|-----------------------------------|-----------------------------------------------|---------------------------------|---------------------------------|------------------------------------------------------|-----------|------------|
| Kreuzer [50] (2016) German uranium miners | Low LET                                       |                                 |                                 | -0.95 [-0.2, 2.06]                                      |           |            |
|                                   | Low LET, adjusted for high LET                 |                                 |                                 | -0.60 [-0.2, 2.82]                                      |           |            |
|                                   | High LET                                       | 58 972                          | 70                              | -5.90 [-0.2, 13.02]                                     | ABM       | 2 years    |
|                                   | High LET, adjusted for low LET                  |                                 |                                 | -3.64 [-0.2, 80]                                       |           |            |
| Kuznetsova [95] (2016) Mayak nuclear workers | All lymphoma                                  | Internal dose (plutonium)       | 23 373                          | 13                                                   | 3.60 [-0.2, 15.17]† | ABM       | 2 years    |
|                                   | MM                                             |                                 |                                 | 3                                                    | 0.03 [ND, ND]†   |           |            |
|                                   | CLL                                            |                                 |                                 | 11                                                   | -0.12 [ND, ND]†  |           |            |
|                                   | NHL                                            |                                 |                                 | 31                                                   | 0.09 [-1.1, 1.45]†|           |            |
|                                   | HL                                             |                                 |                                 | 24                                                   | -0.02 [ND, ND]†  |           |            |
|                                   | MM                                             |                                 |                                 | 11                                                   | 2.39 [-1.1, 5.45] |           |            |
|                                   | CLL                                            |                                 |                                 | 21                                                   | -0.02 [ND, ND]†  |           |            |
| Yiin [91] 2007 uranium workers     | NHL                                            | Whole cohort                    | 29 303                          | 163                                                  | -0.14 [0.2, 0.85] | ABM       | 10 years   |
|                                   | MM                                             |                                 |                                 | 69                                                   | 2.92 [0.5, 7.86] |           |            |
| Study (year)            | Disease | Grouping                  | Sample size (exposed/un-exposed) | Observed Incidence or Mortality | ERR per Gy or Sv for Incidence or Mortality [95% CI] | Dose site | Lag period |
|------------------------|---------|---------------------------|----------------------------------|---------------------------------|------------------------------------------------------|-----------|------------|
| Haylock [96] (2018) UK NRRW radiation workers<sup>c</sup> | NHL     |                           | 707, 353                         | 1.261 [0.08, 2.94], 1.307 [−0.25, 3.77] |                                                      |           |            |
|                        | HL      | Whole cohort (90% male)   | 110, 34                          | −0.588 [-1.94, 8.92]            | 1.307 [−0.25, 3.77]                                   | Badge dose | 10 years   |
|                        | MM      |                           | 167,003                          |                                  |                                                      |           |            |
|                        |         |                           | 277, 175                         |                                  |                                                      |           |            |
| Golden (2019) [173]    | NHL     | Male only                 | 2514                             | 0.20 [–0.23, 0.64]              |                                                      | Thoracic lymph nodes | 10 years   |
| Gillies [92] (2019) UK NRRW radiation workers<sup>c</sup> | CLL     | Male only                 | 173,081                          | −0.60 [−1.69, 0.65]<sup>a</sup> |                                                      | Badge dose | 2 years    |
| Boice [71] (2020) Nuclear weapons test participants | CLL     | Cohort members with dose records | 190                              | −0.66 per 100 mGy [−0.98, 0.85] |                                                      | ABM       | 10 years   |
|                        | MM      |                           | 113,806                          | 350                             | −0.16 per 100 mGy [−1.03, 0.72]                       |           |            |

<sup>a</sup> 90% confidence interval.

<sup>b</sup> Case ascertainment began in 1993 in Russia and Belarus, 6–7 years after exposures.

<sup>c</sup> There is substantial overlap between the NRRW cohort and the UK component of the INWORKS study. ND: not defined or estimated, ABM: active bone marrow.
from MM and 104 from HL, making INWORKS the largest source of information on these diseases. The ERR per Gy for mortality was raised for MM, NHL and HL, though confidence intervals included zero in each case (table 4). In contrast, there was no evidence of increased mortality from CLL (ERR = −1.06, 90% CI: undefined, 1.81), while non-CLL leukaemia mortality was strongly increased (ERR = 2.96, 90% CI: 1.17, 5.21). These and other negative findings for CLL mortality should be interpreted with caution given the indolent and generally non-lethal nature of this disease [100]. The INWORKS results were almost unchanged when including workers with suspected internal exposures (excluded from the 15-country study) or adjusting for socioeconomic status. Excluding UK cohort members reduced the ERR for NHL from 0.47 (90% CI: −0.96, 3.33) to −0.10 (<0, 1.99), while for MM, the ERR was increased from 0.84 (−0.96, 3.33) to 3.32 (0.27, 7.64).

Other large occupational cohorts include Mayak workers [95] and nuclear workers in Japan [93] and Canada [85, 89]. In each case, large central values of ERR are associated with extremely wide confidence intervals, preventing meaningful interpretation. The most recent analysis of the cohort of Rocketdyne workers [88] found no evidence of increased risk of lymphoma, leukaemia or all cancers combined (table 3). Raised risks for NHL [7], MM [64] and, interestingly, CLL [63], have been reported among Chernobyl clean-up workers. The ERR for CLL was 2.58 Gy$^{-1}$ (95% CI: 0.02, 8.43) [63], which although unusual is statistically compatible with the INWORKS study due to overlapping confidence intervals.

Underground miners are exposed to increased levels of alpha-emitting radon progeny, which are known to be associated with lung cancer. Darby et al [86] found no evidence of increased mortality among miners, for either NHL (SMR = 0.80, 95% CI: 0.56, 1.10) or HL (SMR = 0.93, 95% CI: 0.54, 1.48). The SMR for all cancers other than lung was close to background (1.01, 95% CI: 0.95, 1.07). Leukaemia SMR was raised for miners with <10 years employment (1.93) but not ≥10 years (0.99). The leukaemia SMR was reduced from 1.93 to 1.28 after excluding CLL. Studies of uranium miners and mill workers [47–62], exposed to both low LET gamma and high LET alpha radiation, are similarly inconclusive. As with other industry nuclear workers, overall cancer rates tend not to be raised relative to the general population, although there are exceptions [52]. An internal analysis of Eldorado uranium miners by Zablotska et al [60] was also inconclusive. Central ERR values, based on external gamma dose (mean whole body dose = 52.2 mSv), were raised for incidence but not mortality, or vice versa depending on disease subtype (table 4). Confidence intervals were either extremely wide or undefined.

Studies of nuclear weapons test participants [65–71] typically show similar rates of lymphoma, and all cancers combined, to the general population. The most informative study is a recent analysis of a pooled cohort of eight US testing programs [71]. The mean gamma dose was 6 mSv, with 55.3% receiving <5 mSv. The SMR was reduced for NHL and HL (table 3), though this appeared to be driven by a ‘healthy soldier’ effect in the early years of follow-up [71]. Mortality rates for MM were raised among UK test participants in an early study [65] (SMR = 1.17), based on six cases. In a more recent analysis [68], SMR was reduced to 0.96, based on 22 cases. There was little suggestion of raised MM rates in the 8-series US study [71]. The SMR was 0.98 (95% CI: 0.88, 1.09), while an internal analysis yielded an ERR of −0.16 per 100 mGy (95% CI: −1.03, 0.72).

Airline crew are exposed to elevated levels of cosmic radiation, including neutrons and muons, with annual effective doses ranging from 2 to 6 mSv [84]. There is limited evidence of increased incidence or mortality from lymphoma or overall cancer [79–84]. There are some suggestions of raised SMR for lymphoma among male cabin crew, although this appears to be associated with the extremely high rates of AIDS prior to 2000 in this group (mortality for
AIDS was raised 16-fold compared to the general population [83]). A decrease in AIDS prevalence in more recent years may explain the lower SMR for NHL in the most recent analysis of German airline crew [84], compared to previous [81].

The study by Eheman et al [101] is notable for the analysis of lymphoma risk for different subtypes and grades (disease aggressiveness) as part of the Selected Cancers Study. Odds ratios were higher for low-grade lymphoma (1.07, 95% CI: 0.76, 1.50) than for intermediate (0.81, 95% CI: 0.58, 1.13) or high-grade (0.62, 95% CI: 0.3, 1.17) lymphomas. There was some suggestion of higher odds ratios for small cell diffuse lymphomas (1.18, 95% CI: 0.75, 1.90) and follicular lymphomas (1.19, 95% CI: 0.52, 2.75), compared to diffuse large cell lymphomas (0.72, 95% CI: 0.51, 1.00). The large degree of overlap in confidence intervals, however, renders this analysis inconclusive.

A number of studies have focussed on radiologists and radiographers (radiologic technologists), many of whom were exposed to particularly high doses of external low LET radiation in the early decades of medical x-ray imaging. In a recent analysis, Berrington de González et al [77] compared cancer mortality among 34,912 male radiologists to 47,497 male psychiatrists. RRs for all lymphoma (2.83, 95% CI: 1.41, 5.70) and specifically NHL (2.69, 95% CI: 1.33, 5.45) were increased for radiologists graduating before 1940, when doses are thought to have been higher (and follow-up times longer). There was a suggestion, albeit imprecise, of increased RR for all forms of leukaemia (1.91, 95% CI: 0.83, 4.41) for the same time period. There was little suggestion of raised risks for radiologists graduating after 1940, neither for lymphoma, nor for other cancer types. The authors noted lower rates of HIV among radiologists, compared with psychiatrists, potentially resulting in downward bias of risk estimates. A later analysis of physicians likely to perform x-ray guided interventional procedures [78] found no evidence of increased lymphoma risk (RR: 0.77, 95% CI: 0.58, 1.04). In contrast to the LSS, studies of radiographers provide no evidence of any sex difference in mortality or incidence of lymphoma [74, 75].

2.3. Environmental exposures

Studies of natural background radiation [8, 102–108] include populations exposed to both low LET gamma radiation and high LET alpha radiation originating from inhaled radon. Again, with the exception of that due to radon, exposures are reasonably uniform over the whole body. A summary of study findings is presented in table 5.

Tao et al [102] found no evidence of raised rates of lymphoma among residents of the Yangjiang region of China, exposed to elevated background radiation levels, estimated at 6.4 mSv (effective dose) per year. The RR for lymphoma, compared to a neighbouring region with normal background radiation levels, was 0.98 (95% CI: 0.26–3.71). A dose response analysis was attempted by categorising cohort members into low-, medium- and high-exposure groups; however, the results are too imprecise to be informative. Hwang et al [104] reported a raised risk of NHL among residents of buildings in Taiwan made using steel contaminated with cobalt-60 (SIR = 5.4, 95% CI: 1.8, 12.6), though based on just five cases.

No significant associations were detected by Kendall et al [105] between either childhood NHL or HL and gamma or radon background radiation. Positive associations were seen for leukaemia, particularly lymphoid leukaemia, but not for all cancers except leukaemia. Spycher et al [107] also found no evidence of an association between childhood lymphoma and background radiation in Switzerland. Hazard ratios were 1.08, 0.96 and 0.91 for estimated dose rates of 100–150, 150–200 and >200 nSv h\(^{-1}\) versus <100 nSv h\(^{-1}\), respectively, while positive dose responses were observed for leukaemia, CNS tumours and all cancers combined.
Table 5. Summary of studies reporting lymphoma risks from environmental and background exposures.

| Study (year), exposure type, age group | Disease | Grouping | Sample size | Observed Incidence or Mortality | Relative risk (vs. control or unexposed), or Odds ratio [95% CI] | Dose site | Lag |
|--------------------------------------|---------|----------|-------------|-------------------------------|-------------------------------------------------|----------|-----|
| Tao [102] (2000) Yangjiang, China HBRA, All ages | All lymphoma | Low dose | 27 676 | 1 | 0.36 [0.04–3.46] | None stated |
| | | Medium dose | 27 837 | 4 | 1.37 [0.30–6.15] |
| | | High dose | 23 101 | 3 | 1.21 [0.24–6.04] |
| | | All | 78 614 | 8 | 0.98 [0.26–3.71] | Effective (6.4 mSv) |
| Tao [102] (2000) Yangjiang, China HBRA, All ages | NHL | 0–24 Bq m⁻³ | 2226 cases, 3773 controls | 166 | 0.68 [0.43–1.10] | None stated |
| UKCCS [103] (2002) UK Radon exposure, children | NHL | 25–49 Bq m⁻³ | 2226 cases, 3773 controls | 166 | 0.68 [0.43–1.10] | Radon concentration at residence (Becquerel per cubic metre) |
| | | 50–99 Bq m⁻³ | 3773 controls | 0.92 [0.48–1.73] | |
| | | 100–199 Bq m⁻³ | 3773 controls | 0.74 [0.23–2.39] | |
| | | >200 Bq m⁻³ | 3773 controls | 1.57 [0.36–6.92] | |
| | | 0–24 Bq m⁻³ | 72 | 1.00 |
| | | 25–49 Bq m⁻³ | 72 | 0.59 [0.46–1.73] | |
| | | 50–99 Bq m⁻³ | 72 | 1.00 [0.39–2.57] | |
| | HL | 0–24 Bq m⁻³ | 72 | 1.00 |
| | | 25–49 Bq m⁻³ | 72 | 1.00 |
| | | 50–99 Bq m⁻³ | 72 | 1.00 |
| Kendall [105] (2013) UK natural background exposure, children | HL | Gamma⁻ | 27 447 | 939 cases, 1388 controls | 1.04 [0.93–1.16] | Bone marrow 9 months |
| | | Radon⁻ | 36 793 | 983 cases, 1302 controls | 1.07 [0.67–1.70] | |
| | NHL | Gamma⁻ | 36 793 | 983 cases, 1302 controls | 1.04 [0.89–1.21] | |
| | | Radon⁻ | 36 793 | 983 cases, 1302 controls | 1.29 [0.69–2.39] | |
| | Total | Gamma⁻ | 23 199 cases, 32 742 controls | 1.01 [0.93–1.09] | |
| | | Radon⁻ | 23 199 cases, 32 742 controls | 1.14 [0.80–1.62] | |

* RR per mGy cumulative exposure.
* RR per 10³ Bq m⁻³ cumulative exposure. HBRA: high background radiation area, UKCCS: United Kingdom Childhood Cancer Study.
Other studies, including those of children living near nuclear facilities [8, 108] are limited by low case numbers and limited dosimetry (e.g. based on residential distance from the facility).

2.4. Medical radiation—therapeutic

Therapeutic radiation is usually delivered to a localised region, with the remainder of the body exposed to a relatively low dose of scattered radiation. Careful selection of the suitable organ/tissue for dose response analysis is therefore required. Patients with malignant disease may also be treated with chemotherapy, which is known to increase subsequent cancer risk [109]. Some individuals have genetic disorders predisposing them to cancer development and/or increased radiosensitivity (e.g. [110, 111]). Comparison of subsequent cancer rates for patients treated with or without radiotherapy is problematic as treatment choice reflects disease type. Furthermore, apparent associations may also be complicated by therapy-induced immunosuppression [112], especially when radiotherapy is combined with chemotherapy.

Table 6 shows a summary of study findings. Increased rates of lymphoma have been observed among individuals treated with radiotherapy for a previous malignancy [112–115], ankylosing spondylitis [116–118] and peptic ulcer [119] and patients injected with radium-224 (MM) [120]. Studies of patients treated for non-malignant gynaecological conditions [121, 122], otitis serosa (treated with nasopharyngeal radium irradiation) [123] or benign locomotor conditions [124] have found little or no evidence of raised lymphoma risk, though case numbers are small. No association between radioactive iodine-131 (RAI) treatment for hyperthyroidism and lymphoma was found by Holm et al [125] or Franklyn et al [126]. A very small increase in overall cancer incidence was reported in the former study (SIR = 1.06, 95% CI: 1.01, 1.11) but not the latter (SIR = 0.83, 95% CI: 0.77, 0.90). A recent update of a 1998 study [127] of cancer risks among patients treated with RAI for hyperthyroidism by Kitahara et al [128] found RRs, per 100 mGy, of 1.07 and 1.69 for NHL and MM respectively. In both cases, confidence intervals included unity.

A number of studies have made use of Surveillance, Epidemiology and End Results (SEER) data to study risk of lymphoma risk following radiotherapy. Kim et al [112] identified 5590 NHL second malignancies reported by nine SEER registries. RR of NHL was increased for primary malignancies of any type treated with radiotherapy compared to those treated without radiotherapy (RR = 1.13, 95% CI: 1.08, 2.17). When results were analysed by primary disease, positive associations were seen only for non-small cell lung cancer and prostate cancer. No significant difference in NHL risks was seen between males and females. Likewise, there was little evidence of variation in risk between NHL subtypes for all primary cancers combined. Significant differences in RR (versus treatment without radiotherapy) between subtypes were observed, however, for primary cancers of the rectosigmoid, in which diffuse large B-cell lymphoma risks were higher, and thyroid, in which follicular lymphoma risks were higher. Chaturvedi et al [115] identified 52 613 patients among SEER and Scandinavian cancer registries treated with pelvic radiotherapy for cervical cancer. The SIR was raised for NHL (1.20, 95% CI: 1.02, 1.40), based on 157 cases, but not for HL, MM or CLL. In comparison, the SIR for all cancers was 1.34 (95% CI: 1.31, 1.38). Radivoyevitch et al [129] compared CLL/SLL risk among patients treated for non-haematological malignancies using SEER data. RRs were raised among 4483 857 patients not treated using radiotherapy (1.2, 95% CI: 1.17, 1.23) but not raised among 1808 105 patients who were treated with radiotherapy (1.00, 95% CI: 0.96, 1.05). Again, these findings should be interpreted with caution as the types of primary cancer typically treated or not treated with radiotherapy are different and may have inherent different subsequent cancer risks or exposure to other carcinogenic agents (e.g. chemotherapy). Wright
### Table 6. Summary of studies reporting risk of lymphoma following radiotherapy for benign or malignant conditions.

| Study (year) | Disease | Grouping | Sample size (cases/controls) | Observed/Mortality | SIR/SMR [95% CI] |
|--------------|---------|----------|-----------------------------|--------------------|-----------------|
| Darby [116] (1987) | HL | <5 y since Tx | 14 106 | 3 | 2.42 |
| Ankylosing spondylitis | | 5–24.9 y since Tx | 5 | | 1.66 |
| | | >25 y since Tx | 0 | | 0 |
| | | >5 y since Tx | 5 | | 1.32 |
| | NHL | <5 y since Tx | 2 | | 2.03 |
| | | 5–24.9 y since Tx | 13 | | 2.89 |
| | | >25 y since Tx | 3 | | 1.13 |
| | | >5 y since Tx | 16 | | 2.24 |
| | MM | <5 y since Tx | 0 | | 0 |
| | | 5–24.9 y since Tx | 4 | | 1.52 |
| | | >25 y since Tx | 4 | | 1.97 |
| | | >5 y since Tx | 8 | | 1.72 |
| Holm [125] (1991) | All lymphoma | Whole cohort | 10 552 | 28 | 0.72 [0.48–1.03] |
| Hyperthyroidism (I-131) | HL | | | 6 | 0.83 [0.31–1.81] |
| | NHL | | | 22 | 0.68 [0.43–1.04] |
| | MM | | | 21 | 1.05 [0.65, 1.60] |
| Weiss [117] (1994) RT for ankylosing spondylitis | NHL | Whole cohort | 14 109 | 37 | 1.74 [1.23, 2.36] |
| | HL | | | 13 | 1.65 [0.88, 2.81] |
| | MM | | | 22 | 1.62 [1.07, 2.46] |
| Damber [124] (1995) RT for benign locomotor lesions | NHL | <0.20 Gy | 20 024 | 25, 22 | 0.69b, 0.87b |
| | | 0.20–0.50 Gy | | 25, 13 | 1.15b, 0.84b |
| | | >0.50 Gy | | 31, 15 | 1.40b, 0.97b |
| | | Total | | 81, 50 | 1.01 [0.80, 1.25], 0.88 [0.65, 1.16] |
| Study (year) | Disease Grouping | Sample size (cases/controls) | Observed/Mortality | SIR/SMR [95% CI] |
|-------------|-----------------|-----------------------------|--------------------|-----------------|
| HL          | <0.20 Gy        | 8, 9                        | 0.80<sup>b</sup>; 1.34<sup>b</sup> |
|             | 0.20–0.50 Gy    | 3, 2                        | 0.49<sup>b</sup>; 0.48<sup>b</sup> |
|             | >0.50 Gy        | 6, 10                       | 0.96<sup>b</sup>; 2.27<sup>b</sup> |
|             | Total           | 17, 21                      | 0.76 [0.44, 1.22], 1.37 [0.85–2.09] |
| MM          | <0.20 Gy        | 35, 36                      | 1.17<sup>b</sup> |
|             | 0.20–0.50 Gy    | 4, 20                       | 0.75<sup>b</sup> |
|             | >0.50 Gy        | 16, 24                      | 0.86<sup>b</sup> |
|             | Total           | 65, 80                      | 0.96 [0.74, 1.23], 1.25 [0.99–1.56] |
| CLL         | <0.20 Gy        | 19                          | 0.94<sup>b</sup> |
|             | 0.20–0.50 Gy    | 15                          | 1.17<sup>b</sup> |
|             | >0.50 Gy        | 16                          | 1.18<sup>b</sup> |
|             | Total           | 50                          | 1.07 [0.80, 1.41] |

**Carr** [119] (2002) RT for peptic ulcer

| Disease | Grouping | Sample size (cases/controls) | Observed/Mortality | SIR/SMR [95% CI] |
|---------|----------|-----------------------------|--------------------|-----------------|
| NHL     | Whole cohort | 1859                     | 14                  | 1.98            |
| HL      |           | 0                          | 0                  | 1.15            |
| MM      |           | 4                          | 1                  |

**Chaturvedi** [115] (2007) RT for cervical cancer

| Disease | Grouping | Sample size (cases/controls) | Observed/Mortality | SIR/SMR [95% CI] |
|---------|----------|-----------------------------|--------------------|-----------------|
| NHL     | Whole cohort | 52 613/27382               | 157                | 1.20 [1.02–1.40] |
| HL      | (Female only) | 17                         | 1.04 [0.61–1.67]  |
| MM      |           | 71                         | 0.95 [0.75–1.21]  |
| CLL     |           | 44                         | 0.87 [0.63–1.17]  |

**Kim** [112] (2013) RT for all cancers

| Disease | Grouping | Sample size (cases/controls) | Observed/Mortality | SIR/SMR [95% CI] |
|---------|----------|-----------------------------|--------------------|-----------------|
| NHL     | Whole cohort | 1450962                 | 1742               | 1.08            |

<sup>b</sup> SIR/SMR figures not reported in original paper and were calculated based on reported observed/expected numbers. RT: radiotherapy, Tx: treatment, FU: follow-up, mCi: millicurie.
et al [130] found no evidence of increased MM risk among 66,896 patients with pelvic malignancies treated with radiotherapy, compared to 132,372 patients treated without radiotherapy (hazard ratio: 1.08, 95% CI: 0.81, 1.44).

Lymphoma is a relatively uncommon second malignancy among survivors of cancer in childhood or early adulthood (e.g. [131–133]). NHL second malignancies tend to follow a primary diagnosis of HL [134]. Underlying genetic factors and immunosuppression may therefore be the primary risk factor.

### 2.5. Medical radiation—diagnostic

Diagnostic x-ray exposures include general radiography [135, 136], fluoroscopy [137, 138], computed tomography (CT) [39, 139–142], a combination of these [143], or pre-natal x-rays [144, 145]. As with radiotherapy, exposures are usually localised, rather than whole-body. Studies of individuals exposed for diagnostic purposes need to be interpreted with caution due to the potential for reverse causality, where patients are exposed to investigate early symptoms of a later diagnosed cancer [146–148]. Alternatively, some patients may have diseases predisposing them to cancer development. If these individuals undergo more medical imaging tests, the association between radiation and lymphoma may be confounded by indication. A summary of study findings for diagnostic exposures is presented in table 7.

Elevated rates of several forms of cancer have been observed among individuals injected with the alpha-emitting contrast agent Thorotrast [153–155]. Throughout their lifetime, these patients received cumulative absorbed doses of several gray to the bone marrow and several tens of gray to the spleen [154]. A suggestion of an increased risk of NHL was found for a German cohort [153], based on 15 cases (RR versus controls: 2.5), but not for HL or CLL (RR was 0.8 in both cases). The number of cases of lymphoma diagnosed within Swedish [155], Danish [153, 155] and American [155] cohorts are too low to be informative.

Several recent studies have examined lymphoma incidence following diagnostic x-ray exposures before birth or in early childhood. One of the major findings of the Oxford Survey of Childhood Cancers was a raised risk of cancer among children exposed in utero during pelvic radiography [144]. RR (versus unexposed) was raised for lymphoma (1.35, 95% CI: 1.07, 1.65) and for all malignancies combined (1.47, 95% CI: 1.34, 1.62). Foetal doses from obstetric radiography were approximately 10–20 mGy per film [156], though subject to large uncertainties. A large odds ratio was reported by Rajaraman et al [149] for all lymphoma (5.14, 95% CI: 1.27, 20.80) and specifically NHL (6.85, 95% CI: 1.31, 35.70) following diagnostic x-ray exposure in infancy. These findings contrast with those of studies led by Hammer [135] and Baaken [136] in which no evidence of an association was found between lymphoma and post-natal exposure to diagnostic x-rays in a cohort of over 90,000 German children. It should be noted that the average dose received by members of the German cohort was exceptionally low (median estimated effective dose = 0.007 mSv, mean = 0.135 mSv).

A raised incidence rate ratio (IRR) for HL was reported by Mathews et al [139] for 680,000 Australians receiving CT scans before 19 years of age (IRR = 1.15, 95% CI: 1.01, 1.32), based on an exclusion period of 1 year. No association was seen for other lymphoma (IRR = 1.01, 95% CI: 0.82, 1.23), or for lymphoid leukaemia (IRR = 0.96, 95% CI: 0.77, 1.20). The IRR for all lympho-haematological cancer types combined was 1.19 (95% CI: 1.10, 1.29). Hong et al [143] performed a similar study of 1,275,829 Koreans exposed to diagnostic x-rays, including CT, while aged 0–19 years. A raised IRR was reported for NHL (1.66, 90% CI: 1.20, 2.27) based on 41 cases. The IRR for HL was 1.42 (95% CI: 0.90, 2.23), based on 20 cases. Although large, both studies are limited by the potential for reverse causality [146, 157] and lack of dose response analysis. The Australian CT study HL figures contrast with those of Berrington de
Table 7. Studies reporting lymphoma risks following diagnostic medical radiation exposures.

| Study (year), Exposure type, age range | Disease | Grouping | Sample size | Observed incidence/mortality | Measure | Outcome [95% CI] | Lag |
|---------------------------------------|---------|----------|-------------|------------------------------|---------|------------------|-----|
| Bithell, Stewart (1975) [144] Pre-natal x-rays | Lymphoma | Exposed in utero | 719 case control pairs | Relative risk | 1.35 [1.07, 1.69] | |
| Rajaraman [149] (2011) Diagnostic x-rays, children | All lymphoma | Exposed to radiation in utero | 16 cases, 30 controls | Odds ratio | 1.48 [0.66, 3.32] | 1 year |
| | NHL | Exposed to radiation in utero | 13 cases, 18 controls | Odds ratio | 5.14 [1.27, 20.80] | 2 years |
| | All lymphoma | Early infancy radiation exposure | 7 cases, 3 controls | Odds ratio | 1.48 [0.66, 3.32] | 1 year |
| | NHL | Early infancy radiation exposure | 13 cases, 18 controls | Odds ratio | 5.14 [1.27, 20.80] | 2 years |
| Rajaraman [149] (2011) Diagnostic x-rays, children | NHL | Exposed to radiation in utero | 13 cases, 18 controls | Odds ratio | 5.14 [1.27, 20.80] | 2 years |
| | Other NHL | Exposed to radiation in utero | 7 cases, 3 controls | Odds ratio | 1.48 [0.66, 3.32] | 1 year |
| | Whole cohort | Exposed to radiation in utero | 540 cases, 1998 controls | Odds ratio | 0.7 [0.4, 1.3] | 6–12 months |
| Hatcher [150] (2001) Diagnostic x-rays, 30–79 years | MM | ≥20 x-rays compared to <5 | 540 cases, 1998 controls | Odds ratio | 0.7 [0.4, 1.3] | 6–12 months |
| Mathews [139] (2013) CT scans, children | HL | Whole cohort | 680,211 | Incidence rate ratio | 1.70 [1.31, 2.20] | 1 year |
| | NHL (C82–83) | Whole cohort | 680,211 | Incidence rate ratio | 1.70 [1.31, 2.20] | 1 year |
| | NHL (C82–83) | Whole cohort | 680,211 | Incidence rate ratio | 1.70 [1.31, 2.20] | 1 year |
| Journy [140] (2014) CT scans, children | Lymphoma | Unadjusted for PF | 67,274 | Excess relative risk per mGy | 0.008 [−0.057, 0.073] | 2 years |
| | Lymphoma | Adjusted for all PF | 67,274 | Excess relative risk per mGy | 0.008 [−0.057, 0.073] | 2 years |
| | Lymphoma | Adjusted for transplant | 67,274 | Excess relative risk per mGy | 0.008 [−0.057, 0.073] | 2 years |
| | Lymphoma | Adjusted for AT | 67,274 | Excess relative risk per mGy | 0.008 [−0.057, 0.073] | 2 years |
| | Lymphoma | Adjusted for AT | 67,274 | Excess relative risk per mGy | 0.008 [−0.057, 0.073] | 2 years |
| Study (year), Exposure type, age range | Disease Grouping | Sample size | Observed incidence/mortality Measure | Outcome [95% CI] | Lag |
|--------------------------------------|------------------|-------------|-------------------------------------|------------------|-----|
| Krille [141, 151] (2014) CT scans, children | Total | 39 184 | Standardised incidence ratio | 2.96 [1.42–5.45] | 2 years |
| All lymphoma | Excluding PF | 5 | | 1.54 [0.50–3.59] | |
| | One CT scan | 9 | | 3.67 [1.68–6.97] | |
| | >One CT scan | 1 | | 1.08 [0.03–6.02] | |
| Berrington [39] (2017) CT scans, 0–21 y | ABM dose 2 y lag | 178 601 | Excess relative risk | 0.028 [0.024, 0.080] | 2 years |
| HL | Lymphocyte dose 2 y lag | 65 | | −0.001 [−0.016, 0.013] | |
| | ABM dose 5 y lag | | | −0.003 [−0.027, 0.022] | |
| | Lymphocyte dose 5 y lag | | | | |
| Harbron [138] (2018) Cardiac catheterisations, 0–22 y | All lymphoma | 22 | Standardised incidence ratio | 9.15 [5.66–13.97] | |
| NHL | Whole cohort | 11 270 | | 19.49 [11.39–31.10] | 2 years |
| HL | | 4 | | 2.70 [0.68–7.07] | |
| All lymphoma | Transplant recipients censored, post-transplant | 0 | | 0 | |
| NHL | | 0 | | 0 | |
| HL | | 0 | | 0 | |
| Baaken [136] (2019) Diagnostic x-rays, children | All lymphoma | Whole cohort | Incidence ratio | 0.61 [0.25, 1.26] | 2 years |
| HL | | 92 998 | | 0.21 [0.01, 1.16] | |
| NHL | | | | 1.35 [0.44, 3.16] | |
| All lymphoma | 0 to <10 μSv | 3 | Incidence rate ratio | 1.18 [0.18, 7.53] | |
| NHL | | | | 1.17 [0.18, 7.55] | |
### Table 7. (continued)

| Study (year), Exposure type, age range | Disease | Grouping | Sample size | Observed incidence/ mortality Measure | Outcome [95% CI] | Lag |
|--------------------------------------|---------|----------|-------------|--------------------------------------|-----------------|-----|
| Hong [143] (2019) Diagnostic x-rays, children | HL      |          |             |                                      | 1.32 [0.85, 2.05] |     |
|                                       |         |          |             |                                      | 1.73 [1.28, 2.32] | 2 years |
|                                       |         |          |             |                                      | 1.27 [0.97, 1.66] |     |
|                                       | Other lymphoma | Whole cohort | 1 275 829 (e), 10792 992 (u) | 47 | Incidence rate ratio | |
|                                       | Other lymphoid |          |             |                                      | 0.83 [0.71, 0.97] |     |
|                                       | <1 mGy vs >1–5 mGy ABM dose | 679 cases, 710 controls |             |                                      | 0.61 [0.50, 0.74] | 2 years |
| Pasqual [152] (2020) All lymphoma<1 mGy vs 5–15 mGy |          |          |             |                                      | 0.60 [0.42, 0.85] |     |
|                                       | <1 mGy vs >15 mGy | 61 cases, 88 controls |             |                                      |             |     |

*ICD-10 Codes 82–83 represent follicular and non-follicular B-cell NHL, codes 84–90 represent T/NK NHL, other B-cell lymphomas and MM.

*Excluding Burkitt’s lymphoma.

*Exposures up to 12 months from interview date, which was within 6 months of diagnosis, AT: ataxia telangiectasia, PF: predisposing factors, ABM: active bone marrow.
González et al [39], who found no association between HL and estimated bone marrow or lymphocyte dose from CT scans in childhood. This analysis was based on the same UK cohort in which positive association were found for leukaemia/myelodysplasia and brain tumours [158, 159]. Studies based in France [140, 160] and Germany [141, 151] found little evidence of raised risk of lymphoma following CT scans in childhood after excluding individuals with predisposing syndromes. A recent case control study [152] found no evidence of an association between lymphoma risk and self-reported lifetime medical x-ray exposure, for 2362 cases compared to 2465 controls. Cumulative estimated bone marrow doses were very low, however (median: 2.25 mGy).

Raised lymphoma rates have been reported among individuals who underwent fluoroscopically guided cardiac catheterisation procedures in childhood or early adulthood [137, 138]. A recent analysis [138] found elevated rates of both NHL (SIR = 19.49 95% CI: 11.39, 31.10) and HL (SIR = 2.70 95% CI: 0.68, 7.07). Following transplant registry linkage, it was found that all malignant lymphoma cases and nine cases of lymphoproliferative disease developed post-transplant. The proportion of transplant recipients in this cohort (around 5%) is likely to be much higher than in other medical radiation exposure studies, given the high proportion of patients with serious cardiac abnormalities.

3. Discussion

Lymphoma is frequently included in site-specific analyses of cancer risks following radiation exposure. Yet this disease is, perhaps, the most challenging form of cancer to analyse in radiation epidemiology studies. This is due to (1) the high degree of heterogeneity among lymphoid malignancies, with potential for irregularities in grouping between epidemiological studies, (2) uncertainty in the site of initiation, and (3) the profound impact of infection and immune system compromise on lymphoma risk. Partly for these reasons, evidence of an association between lymphoma and ionising radiation exposure has been inconclusive [42, 43]. Issues (2) and (3) suggest a greater weight should be placed on studies of healthy populations receiving approximately whole-body exposures, including atomic bomb survivors, radiation workers and those exposed to elevated background radiation levels. While external comparisons typically show lymphoma rates similar to the general population, internal analyses tend to suggest a dose-dependent excess lymphoma risk. Confidence intervals are wide, however, indicating highly imprecise risk estimates. There is no evidence that RRs for lymphoma are any higher than for other types of cancer and appear to be lower than for leukaemia.

Studies also suggest a small excess risk of lymphoma following radiotherapy for malignant or non-malignant conditions. This is hardly surprising as almost all cancer types appear to be inducible by radiation if the dose is sufficiently high. Lymphoma risk is increased by a factor of around 5–10 among adult transplant recipients and up to 100 in people with HIV/AIDS [21], i.e. much higher risks than observed among individuals treated with radiotherapy (<2-fold). This suggests the impact of radiation and radiation-induced immunosuppression is relatively minor compared to the long-term immunosuppression associated with transplantation (drug-induced) or AIDS. Effect modification, or an interaction between immunosuppression and radiation remains a possibility, however.

There is little evidence of any difference in lymphoma risk for acute versus chronic radiation exposures, or for high versus low LET, or internal versus external exposures, for a given absorbed dose. Risks are similar for male atomic bombing survivors exposed at a very high rate, and nuclear workers receiving protracted exposures. There are insufficient data to determine the impact of age at exposure on lymphoma risks.
The higher lymphoma ERR among male atomic bombing survivors is puzzling and lacks a biological explanation. No such pattern was observed for MM in the same study [45], or in studies of medical radiographers [74, 75]. In each case, confidence intervals for male and female ERR figures overlap, suggesting any apparent sex differences in the LSS could be a chance finding. Lymphoma mortality was reported to be higher among male airline cabin crew than female [80], although this may be largely explained by much higher rates of AIDS in the former group.

The classification of lymphoma and other lymphoid malignancies has evolved considerably over the last 50 years, in parallel with advancements in understanding of the differentiation of immune cells and cell of origin [2, 161–164]. Overviews of current and historical classifications, including compatibility between systems, are presented elsewhere, e.g. [12, 165]. For the purposes of this review however, the important consideration is whether the distinction between lymphoma subtypes, or between lymphoma and lymphoid leukaemia, could influence apparent radiation-associated risks. For example, in the analysis of childhood cancer in the vicinity of nuclear facilities, some cases were initially classified as NHL before being reclassified as leukaemia [8]. Misclassification, or inconsistencies in classification, could potentially explain unusually high risks for lymphoma but not leukaemia (e.g. [149]), or vice versa. In this regard, there may be some justification for grouping all lymphoid malignancies together [8, 166].

However, there is known heterogeneity in non-radiogenic risk factors within the broad subgroups of lymphoid malignancies (e.g. [22]). NHL, for example, is almost invariably analysed as a whole, despite potential differences in cell of origin, proliferating cell type and disease aggressiveness. Given that ALL is strongly associated with radiation (e.g. [46]) it may be assumed that LBL, which is histologically the same disease in mass lesion form, is similarly sensitive to induction by radiation. Yet ALL and LBL have different ICD [11] and ICD-O [12] codes and are likely to be assigned as leukaemia or lymphoma, respectively, in epidemiological analyses. Likewise, SLL and CLL are regarded as the same disease in solid and circulating form, respectively. Again, partly due to the different ICD coding, it is possible these diseases have been analysed separately in epidemiology studies, with SLL likely assigned as NHL.

Many forms of lymphoma are associated with good prognosis, with 5-year survival rates exceeding 80% for HL and 70% for CLL [167]. Richardson et al [100] note that CLL is often not listed as the primary cause of death, or even mentioned on death certificates. The use of mortality data may, therefore, be less reliable than incidence data. This could potentially explain the apparent lack of association between radiation exposure and CLL [100].

There is some suggestion that lymphoma may have a long latency period, potentially further explaining negative CLL findings [100, 168] and the relatively late appearance of raised risks in the LSS and Savannah River cohorts [38]. In contrast to other mature lymphoid malignancies, both CLL and myeloma are almost exclusively diseases of middle and old age, with around 99% of cases being diagnosed after age 50 years [16, 18]. Many of the cohorts, especially those of medically exposed individuals, lack sufficiently long follow-up periods to provide meaningful information on these diseases. The reverse may also be true, however. Lymphomas are occasionally classed as ‘solid tumours’ in epidemiological studies, meaning exclusion periods and dose lagging for lymphoma analyses are the same as for other solid tumours such as lung cancer (typically 5 or 10 years). However, histologically, lymphoma has more in common with leukaemia, a disease known to occur relatively early following radiation exposure (CLL possibly being the exception). One may assume acute leukaemia-like forms of lymphoma such as LBL may also develop similarly early. Again, the standard grouping of diseases may obscure meaningful patterns.
Ongoing studies involving large pooled cohorts hold promise for improved information on lymphoma risks following radiation exposure. The Million Worker Study (MWS), coordinated by the National Council on Radiation Protection and Measurements, includes atomic weapons test veterans, US Department of Energy workers, nuclear power plant workers, industrial radiographers and medical radiation workers [169, 170]. The MWS will provide unprecedented information on risks from protracted exposures, based on analysis of over 300,000 deaths.

In addition, a number of large cohorts will provide improved information on lymphoma risks from exposures in childhood. The MEDIRAD study (https://www.medirad-project.eu/) involves a pooled cohort of children and young adults who received CT scans in Europe, continuing from the EPI-CT study [171]. The newly launched HARMONIC study [172] (https://harmonicproject.eu/) will examine the long-term effects of cardiac catheterisations and proton beam therapy in children. Given the high rates of heart transplantation in the former group, obtaining information on transplants (ideally through registry linkage) will be essential for this study.

4. Conclusion

The association between ionising radiation exposure and lymphoma, including MM and CLL, is complex and subject to large uncertainties. Increased risks for certain lymphoma subtypes may be obscured by broad classification schemes or confounded by the impact of immunosuppression or infection. The available evidence suggests a positive dose-dependent association between radiation exposure and lymphoma risk. This association appears to be stronger for males and stronger for NHL, as opposed to Hodgkin’s lymphoma, MM or CLL. The risk of radiation-induced lymphoma is unlikely to be especially large, certainly no higher than for other cancer types. For populations in which lymphoma rates are unusually high, other aetiologies should be considered first, especially if rates for more radiogenic cancers are not raised.

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Conflict of interest

We have no conflicts of interest to declare.

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