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Ionizing radiation exposures in treatments of solid neoplasms are not associated with subsequent increased risks of chronic lymphocytic leukemia

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ABSTRACT

Exposure to ionizing radiation is not thought to cause chronic lymphocytic leukemia (CLL). Challenging this notion are recent data suggesting CLL incidence may be increased by radiation exposure from the atomic bombs (after many decades), uranium mining and nuclear power facility accidents. To assess the effects of therapeutic ionizing radiation for the treatment of solid neoplasms we studied CLL risks in data from the Surveillance, Epidemiology, and End Results (SEER) Program. Specifically, we compared the risks of developing CLL in persons with a 1st non-hematologic cancer treated with or without ionizing radiation. We controlled for early detection effects on CLL risk induced by surveillance after 1st cancer diagnoses by forming all-time cumulative CLL relative risks (RR). We estimate such CLL RR to be 1.20 (95% confidence interval, 1.17, 1.23) for persons whose 1st cancer was not treated with ionizing radiation and 1.00 (0.96, 1.05) for persons whose 1st cancer was treated with ionizing radiations. These results imply that diagnosis of a solid neoplasm is associated with an increased risk of developing CLL only in persons whose 1st cancer was not treated with radiation therapy.

1. Introduction

Chronic lymphocytic leukemia (CLL) risks in Japanese exposed to ionizing radiation from the atomic bombs are approximately at background levels [1] or, with longer follow-up, perhaps marginally above background levels [2]. CLL is, however, far more common in persons of predominately European descent than in Japanese [3], probably because of genetic differences between the populations [4,5]. In populations of predominately European descent CLL risks were not significantly increased among radiation-monitored workers [6,7], people exposed to radioactive waste in the Techa River area of Russia [8], Canadian uranium miners [9], women treated with radiation therapy for cervical [10], uterine [11] or breast [12] cancers, or people treated with radiation therapy for benign diseases [13,14]. CLL risks were however slightly elevated in persons with prostate cancer (treated with radiation or not) [15], in Czech uranium miners [16] and in Chernobyl cleanup workers [17]. There have been no reports about the relationship between radiation therapy for cancer and subsequent risks of CLL in Surveillance, Epidemiology, and End Results (SEER) data [18].

The risk of CLL as a 2nd cancer can be above background levels because of inherited predisposition, environmental exposures, 1st cancer treatment(s), or combinations thereof [19]. Because of increased surveillance after 1st cancers, and because CLL often displays an indolent course with substantial numbers of cases diagnosed coincidentally, CLL may be diagnosed as a 2nd cancer earlier in its natural history than CLL as a 1st cancer. This is expected to cause excess CLL 2nd cancer cases immediately after 1st cancer diagnoses and a subsequent trough that is missing those excess cases. If the 1st cancer or its treatment increases CLL risks, trough magnitude decreases are expected. Conversely, if the 1st cancer or its treatment decreases risks of CLL, trough magnitude increases are expected. Using SEER data [18] we report estimates of time courses of CLL 2nd cancer relative risks (RR = observed/expected cases) after diagnoses of non-hematologic 1st cancers treated with or without radiation. As metrics of cancellation of initial RR peaks by subsequent troughs we also provide estimates of net cumulative CLL RR,

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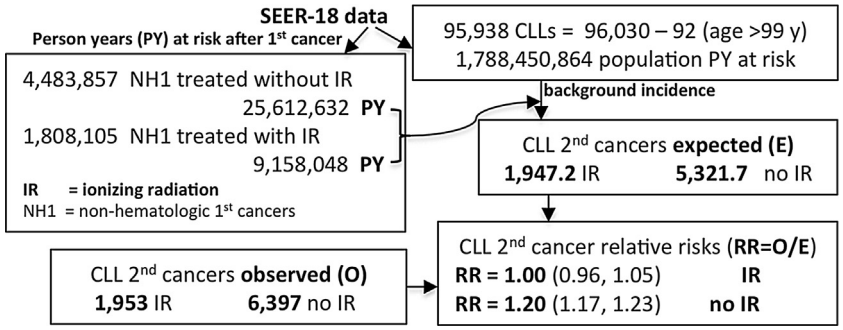

Fig. 1. Workflow. Top: all 18 SEER registries were used. Left branch: non-hematologic 1st cancers yield PY at risk of a 2nd cancer. Right branch: all cases and population PY yield background incidence rates. The left and right branches merge to yield expected 2nd cancer cases (E) and thus relative risks RR = O/E where O is the observed number of 2nd cancer cases. Values shown are for both sexes combined.

i.e. RR calculated using all times after 1st cancers. Our goal was to determine if such net RRs associate with 1st cancer radiation therapy.

2. Materials and methods

We used SEER data [18] through 2012 with CLL and small lymphocytic lymphoma (SLL) defined by ICD-O3 codes 9823 and 9670 pooled because they are biologically equivalent despite minor differences in clinical presentation [20] and because increased surveillance after a 1st cancer may otherwise cause some CLL/SLL cases that would have been first diagnosed as CLL to instead be diagnosed with lower blood lymphocyte levels consistent with SLL (an absolute monoclonal B-cell lymphocyte count of >5000 cells/mL distinguishes CLL from SLL). Cases treated with ionizing radiation were defined by SEER radiation codes 1–6 and those not treated with radiation were defined by codes 0 or 7, *i.e.* radiation types were pooled and radiation doses were approximated as present or absent; cases with SEER radiation codes 8 and 9 (radiation status unknown) were excluded as were 1st cancers of hematologic origins (defined in Supplementary Section S1) and those with unknown survival times (out of 8,677,429 cases in SEER, 101,584 have unknown survival times, 229,569 have unknown radiation status, and 78% of those missing survival information are also missing radiation information, so less than 3% of cases were excluded due to unknown survival or radiation status). Data were analyzed using the R package SEERaBomb [21], which computes person-years (PY) at risk of 2nd cancers based on 1st cancer survival time, age at 1st and 2nd cancer diagnoses, and starts and ends of user-specified time-since-1st-cancer-diagnosis intervals. SEERaBomb multiplies such PY into age-, sex- and year specific background incidence rates formed as surface splines fitted by Poisson regression to all SEER cases and population PY, to yield expected 2nd cancers (E) and thus relative risks RR = O/E where O is the observed number of 2nd cancers. This workflow [21] is depicted in Fig. 1, which also shows numbers of cases and PY involved (with sexes pooled). RR 95% confidence intervals (CI) were computed as qchisq(.025, 2*O)/(2*E) and qchisq(.975, 2*O + 2)/(2*E) in R, assuming O is Poisson distributed [22]. Additional details can be found in our R scripts (Supplementary Section S2). Limitations of our study include lack of anti-cancer drug data in the SEER dataset, radiation therapy only considered as a binary value (yes or no), with no information on energy, dose, duration, fields or schedule, and the availability of only data on the initial anti-cancer intervention (relapse therapy information is not provided).

3. Results

3.1. CLL risk time courses after non-hematologic cancers

To determine if persons with non-hematologic 1st cancers treated with radiation are more likely to develop CLL we analyzed CLL 2nd cancer RR dynamics in SEER data. RR time courses displayed a *paroxysmal* increase approximately independent of radiation,

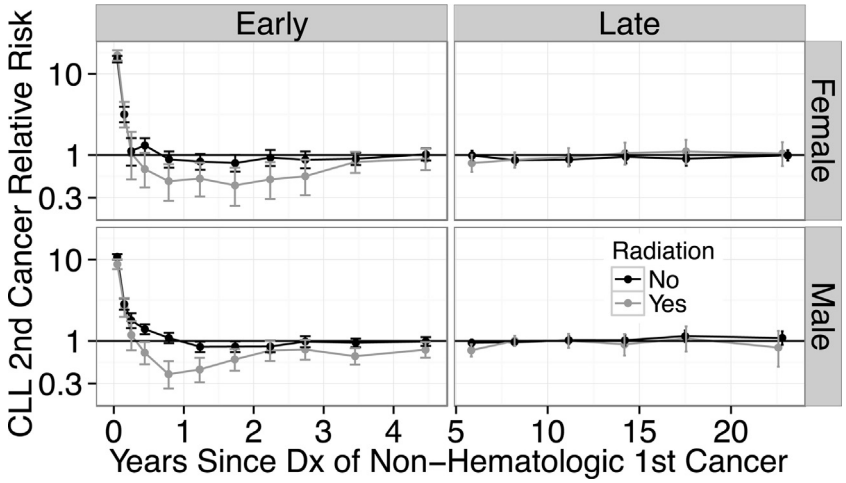

Fig. 2. CLL RR time courses after all non-hematologic 1st cancers. Troughs are apparent after 1st cancers treated with radiation. Initial peaks are similar in persons treated or not with radiation. Troughs resolve to background levels (RR = 1) in 7–8 y. Times are PY-weighted means in (0,0.1), (0.1,0.2), (0.2,0.3), (0.3,0.6), (0.6,1), (1,1.5), (1.5,2), (2,2.5), (2.5,3), (3,4), (4,5), (5,7), (7,10), (10,13), (13,16), (16,20), and >20 y.