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Are we ready to predict late effects? A systematic review of clinically useful prediction models

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Abstract

Background—After completing treatment for cancer, survivors may experience late effects: consequences of treatment that persist or arise after a latent period.

Purpose—To identify and describe all models that predict the risk of late effects and could be used in clinical practice.

Data sources—We searched Medline through April 2014.

Study selection—Studies describing models that 1) predicted the absolute risk of a late effect present at least one year post-treatment, and 2) could be used in a clinical setting.

Data extraction—Three authors independently extracted data pertaining to patient characteristics, late effects, the prediction model, and model evaluation.

Data synthesis—Across fourteen studies identified for review, nine late effects were predicted: erectile dysfunction and urinary incontinence after prostate cancer; arm lymphedema, psychological morbidity, cardiomyopathy or heart failure, and cardiac event after breast cancer; swallowing dysfunction after head and neck cancer; breast cancer after Hodgkin lymphoma; and thyroid cancer after childhood cancer. Of these, four late effects are persistent effects of treatment and five appear after a latent period. Two studies were externally validated. Six studies were

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designed to inform decisions about treatment rather than survivorship care. Nomograms were the most common clinical output.

Conclusion—Despite the call among survivorship experts for risk stratification, few published models are useful for risk-stratifying prevention, early detection, or management of late effects. Few models address serious, modifiable late effects, limiting their utility. Cancer survivors would benefit from models focused on long-term, modifiable, serious late effects to inform the management of survivorship care.

Keywords

neoplasms; survivors; risk; decision support techniques; secondary prevention

Introduction

Due to improved screening, early detection, and treatment, people with a diagnosis of cancer are living longer than ever before. Unfortunately, the consequences of the cancer and its treatment – late effects – threaten the health and quality of life of cancer survivors. Late effects include both persistent sequelae of treatment (long-term effects) and conditions that develop after a latent asymptomatic period (late-occurring effects). The prevention, early detection, and management of late effects pose a significant challenge to survivors and their healthcare providers. In the United States, 13.7 million individuals have ever been diagnosed with cancer, 64% of whom were diagnosed at least 5 years ago.(1, 2) This large and heterogeneous group of survivors will differ in their long-term needs, requiring different intensity of follow-up. For survivors who underwent chest radiation for Hodgkin lymphoma, it is not clear who would benefit most from routine breast cancer screening. Similarly, for patients who received anthracycline chemotherapy, it may be appropriate for oncologists to routinely monitor cardiac function for some patients to detect early signs of cardiovascular disease – but not all patients, given the harms of overdiagnosis, the costs, and the resource intensity that can be associated with cardiac monitoring.

Because healthcare needs vary widely among cancer survivors, there has been a call for personalized care tailored to individual needs.(3, 4) Survivorship experts have promoted risk stratification to determine the intensity and setting for post-treatment follow-up.(5) The Institute of Medicine recommends lifelong “risk-based” health care for all childhood cancer survivors.(6) This entails a systematic plan for periodic screening, surveillance, and prevention that is adapted to the risks arising from the cancer, its therapy, genetic predispositions, lifestyle behaviors, and comorbid conditions.(6, 7) Survivors at highest risk for serious late effects may require frequent monitoring or management, while those at lower risk may not benefit from such intensive follow-up. Indeed, overutilization of intensive follow-up for low risk survivors may be costly and lead to overdiagnosis. Similarly, depending on the late effect, survivors at highest risk may be most appropriately managed by their oncology team or specialized survivorship clinics, while lower risk survivors could safely transition their care to a well-informed primary care provider.

In order to risk-stratify cancer survivorship care, clinicians need tools to identify patients at high risk for serious late effects. Such tools include simple algorithms (such as referring all

patients who receive chest radiation for cardiovascular screening) or models that incorporate multiple variables (risk prediction modeling). Risk prediction modeling is a general term to describe mathematical methods of estimating individualized risk among patients. Ideally such models are developed among one group of people and then externally validated among a different, independent group of people to measure the appropriateness of extrapolating findings. When external validation is not feasible, internal validation uses mathematical methods to correct for optimism, mitigating the dangers of overstating findings from a single study population. Clinical risk prediction models are intended to be useful in a medical setting, where a healthcare provider can use a patient's clinical data to calculate an absolute risk of an event occurring. The clinician can then use risk information to direct care, and cancer survivors can use their personalized risk to guide self-management. In order to have a feasible clinical risk prediction model, parsimony is critical. It is important that models include only the parameters that are accessible to the clinicians who are using the model to make decisions. Our goal was to identify and describe all existing models that predict the risk of late effects and could be used by clinicians to risk-stratify the care of cancer survivors. We conducted a systematic review of the literature to identify and summarize such models, focusing on characterizing whether the model is ready for use in clinical practice.

Methods

Data Sources and Searches

We systematically searched MEDLINE from inception through April 2014 for studies meeting eligibility criteria. We required that studies include a statistical method that predicted the absolute risk of a late effect that was present at least one year post-treatment. We did not include studies that predicted recurrence, unless recurrence was combined with a late effect as the study outcome. We only included studies with models that clinicians who did not treat the patient could use to calculate a predicted probability of one of more specific late effects, even if this was not the explicit intended use of the model. Some studies assessed outcomes both before and after one year post-treatment; for long-term effects, we only included those studies for which the outcome was likely to be present at one year following treatment completion and remain present for a significant period of time. For late-occurring effects, we only included those studies for which the outcome was also likely to be present at one year or later following treatment completion and remain present for a significant period of time. That is, because the time frame could include acute effects of treatment, the duration of the condition needed to be long enough to merit prediction and management in the post-treatment setting. Non-English studies were excluded.

We used exploded MeSH terms and keywords to identify two main topics: (1) *prediction models, nomograms, absolute risk, or model validation* among people with (2) *neoplasms*. The full search strategy is in the Appendix. We did not use any terms to specify cancer survivors or late effects, because we did not want to exclude studies that did not use terms relating to these topics in their title or abstract. We manually reviewed the references of included studies to identify additional studies.

Study Selection

In order to assess the eligibility of studies, two authors evaluated the titles and abstracts and excluded clearly ineligible papers. The same authors screened the full text of each remaining article in a blinded duplicate fashion. Any discrepancies that arose were solved through discussion among authors.

Data Extraction and Quality Assessment

Two authors extracted data from each included study using a standardized data collection form in a blinded duplicate fashion. We reported study data that could inform whether the study methodology was sound, whether the model is usable in clinical practice, and whether the model is useful for survivors and their providers. Specifically, we collected information related to 1) study design and characteristics, 2) types of late effects studied, and 3) details of the prediction modeling methodology, including sample size, whether the model was validated, whether validation was internal or external (we categorized split-sample validation and assessments of sensitivity and specificity as internal validation), output style, and public availability of the model. Similarly, we evaluated whether discrimination was reported for internal validation and whether discrimination and calibration were reported for external validation. Discrepancies were resolved by consensus.

Results

The search yielded 278 potentially eligible studies for full-text screening. (Figure) We subsequently excluded 137 studies that did not measure an outcome at one year or later or studies measuring acute outcomes that were unlikely to be present at one year. We also excluded 42 studies that presented a risk prediction model but did not present a usable tool for clinicians. Twenty-eight of these 42 studies were radiation dosimetry studies intended for determining optimal dosing; such models required detailed dosing data that could not feasibly be used by non-specialists in the survivorship setting. After full-text screening and review of references of included studies, fourteen studies were eligible for review. The Table describes characteristics of the included studies, including data sources, study sample, model development, and validation.

Late effects

A total of nine unique late effects comprised the outcomes for the models in the fourteen eligible papers: erectile dysfunction and urinary incontinence after prostate cancer; arm lymphedema, heart failure or cardiomyopathy, cardiac event, and psychological morbidity after breast cancer; swallowing dysfunction after head and neck cancer; breast cancer after Hodgkin lymphoma; and thyroid cancer after childhood cancer. Of these, four late effects represent persistent effects of treatment (erectile dysfunction, urinary incontinence, psychosocial morbidity, and swallowing dysfunction), and the models measured the risk of these effects remaining present after a defined period of time. The remaining five late effects (arm lymphedema, heart failure or cardiomyopathy, cardiac event, breast cancer, and thyroid cancer) represent late-occurring effects that appear after a latent period. Prevalence of late effects ranged from 1.3% (thyroid cancer after childhood cancer) to 65% (erectile

dysfunction after prostatectomy).(8–19) Two studies of sexual function after treatment for prostate cancer did not report prevalence.(20, 21)

Timing of late effects

All studies investigated late effects between 6 months and 30 years after treatment completion. Eight of the fourteen studies investigated the presence of late effects solely within the first three years.(9, 11–13, 15, 19–21)

Statistical models

All studies in this review used multivariable regression analyses to determine the risk of late effects. Only two were externally validated, and calibration and discrimination were assessed.(15, 16) None of the studies were themselves validation studies. Ten of the remaining twelve studies were internally validated, using split sample, cross-validation, or bootstrap techniques to correct for optimism.(8, 11–14, 17–21) One study was a metaanalysis of multiple studies of erectile dysfunction, which was limited by poor study design (failure to account for between-study variability).(10)

Model purpose

Many of the studies in this review were implicitly or explicitly designed to inform cancer-directed treatment decisions rather than survivorship decisions.(10, 12, 13, 17, 18, 20) An example is the study by Romond et al., in which the authors suggest that their clinical risk score can be used to balance the benefits and harms of adding trastuzumab to the standard chemotherapy regimen in breast cancer.(17) One application to survivorship is the use of the prediction model for patient counseling and setting expectations.(15) Six studies described clinical uses for their model in the post-treatment setting.(8, 11, 14, 16, 19, 21) The studies by Bevilacqua et al. (on lymphedema) and Gallina et al. (on erectile function) discussed using models to identify patients at highest risk in order to target therapies for late effects.(14, 21) Kovalchik et al. and Ezaz et al. predicted occurrence of a late effect (second primary thyroid cancer and cardiomyopathy, respectively) with the goal of stratifying monitoring efforts in the survivorship period.(16, 19) Ganz et al. developed a model of psychosocial morbidity after breast cancer treatment.(11) The authors stated that the intended goal was to target resource-intensive psychosocial screening and counseling to those at highest risk of poor outcomes. Travis et al. predicted late-occurring breast cancer after treatment for Hodgkin lymphoma, with findings intended to inform counseling and clinical management of survivors.(8)

Clinically useful output

The most common user interface of the models was a nomogram, presented in five studies.(10, 12, 14, 18, 21) The nomograms graphically combine levels of risk factors to yield a total point score corresponding to an absolute risk of a late effect. The remaining studies used different presentations for calculating risks. Alemozaffar et al., Travis et al., and Chipman et al. each presented a table of predicted risks based on the selected risk factors from the model.(8, 15, 20) Briganti et al. presented a method of categorizing patients based on risk factors, and corresponding Kaplan Meier curves show predicted erectile function

recovery for each risk category.(13) Similarly, Romond et al. presented an equation based on risk factors that yields a risk score that corresponds to a predicted risk of cardiac event on a figure.(17) Ezaz et al. converted regression coefficients to a point system that correspond to absolute risk of heart failure or cardiomyopathy found in a table.(19) Ganz et al. developed a decision tree to show the absolute risk of psychosocial morbidity.(11) Kovalchik et al. used regression modeling results to create a downloadable electronic calculator to predict the risk of thyroid cancer.(16) Lastly, Langendijk presented a risk scoring system based on the regression output.(9)

Discussion

Despite the call among survivorship experts for risk stratification, very few papers have been published that are useful for risk-stratifying prevention, early detection, or management of late effects. In fact, most of the studies in our review are primarily intended to inform risk-benefit discussions before cancer treatment (if the intention was stated at all), but they could be adapted for use in a survivorship setting.(9, 12, 13, 15, 17, 18, 20)

In response to the British National Cancer Survivorship Initiative's endorsement of risk stratification for cancer survivors, Watson et al. laid out a framework for risk stratification among cancer survivors.(22) The authors modify the criteria of Wilson and Junger, originally put forth to identify conditions for which mass screening is appropriate and effective.(22) In the modified Wilson and Junger criteria, the condition being predicted should be an important health problem with an existing effective intervention. This criterion, among others balancing benefits and harms, describes appropriate targets for predicting risk among cancer survivors.

There are numerous late effects identified in the literature, many of which are common and would qualify as important health problems with existing effective interventions.(1, 23) Examples include carotid stenosis after radiation to the neck and osteoporosis among recipients of hormone therapy following prostate cancer. Despite the presence of late effects that are appropriate for prediction, few models exist. This may be due in large part to the lack of detailed data and long-term follow-up of toxicities in adult cancer survivors, which contributes to the difficulty in developing and validating prediction models of late effects. Relatedly, most models we identified did not have long-term follow-up. Only five studies predicted late effects occurring at least five years from treatment.(8, 14, 16–18) Short time horizons limit the utility of prediction models in stratifying care for cancer survivors, particularly regarding late effects that can have a latency longer than five years. Confronted with limited resources, the development of new risk models will require strategic leveraging and supplementing of existing data and infrastructures, to address high-priority clinical events.(24) Extending the follow-up of existing clinical trials could permit the study of late effects, as long as meaningful outcomes are routinely collected over time. Another approach is to enhance institutional databases to uniformly collect data on relevant late effects identified during routine post-treatment follow-up.

Most of the models identified address late effects that persist after treatment, such as swallowing dysfunction after radiation for head and neck cancer and renal insufficiency

after surgery for renal cancer. Models of persistent long-term effects have potential utility for both clinicians and survivors. Predicting the continued presence of erectile dysfunction at three years, as Briganti and colleagues do, may help in establishing appropriate management (or appropriate expectations) for survivors, as severity and time course of erectile function recovery may vary by individual.(13)

However, Watson et al. specify that a latent period should be present in order to merit risk stratification.(22) Predicting a late effect that occurs after an asymptomatic latent period serves a different and arguably more important purpose. In a population of asymptomatic survivors, it may be difficult to distinguish who needs more intensive monitoring or intervention. Risk prediction may be particularly useful in stratifying the care of asymptomatic patients with complicated risk profiles. The study by Romond and colleagues took this approach of modeling the risk of a cardiac event five years after trastuzumab (Herceptin) treatment for breast cancer.(17) Although the authors intended the model to inform whether the addition of trastuzumab to traditional therapy is worth the risk of cardiac toxicity, the model could inform the management of breast cancer survivors moving forward from treatment completion.

The prediction of life-threatening effects is a critical next step in improving the health of cancer survivors. Psychosocial morbidity, erectile dysfunction, and sexual dysfunction (all found in our review) are serious and bothersome late effects that can significantly impair quality of life. However, only rarely are any of these late effects life-threatening. Swallowing dysfunction, second cancers, and heart disease, which are all outcomes of existing prediction models, are all arguably more dangerous late effects.

Life-threatening late effects are only worth modeling, however, if they are potentially modifiable. Although there is an excess risk for secondary sarcoma following high dose therapeutic radiation for a childhood or young adult cancer, there is not a screening test to detect an early asymptomatic phase. Thus, frequent monitoring for a secondary sarcoma likely has little value, even among high-risk patients.(25) Similarly, for swallowing dysfunction, few prevention and modification options exist. Education about self-care may be the most important intervention to target people at high risk for such late effects with limited prevention opportunities.

A final consideration is that prediction models are only useful when survivors are likely to live long enough to experience the late effect. Beyond the typical metric of 5-year survival, this information can be difficult to find. There is a growing literature on conditional survival, which is a relevant metric for longer-term survivors and can inform both the likelihood of experiencing late effects and the importance of intervention.(26–29) More work in this area will help identify survivors who can benefit most from the prediction of late effects.

Ultimately, the most benefit will come from modeling late effects that are serious, have a latent period, may respond to early intervention, and apply to a large population of survivors. An example of a good target for risk prediction is heart disease after chest radiation. A risk prediction model for heart disease could identify a high-risk subpopulation,

among whom aggressive risk reduction measures or frequent cardiac monitoring may be most effective. There is also a clear role for research in identifying and refining optimal interventions among high-risk survivors.

There are caveats to modeling late effects among survivors. First, researchers are still clarifying the associations between cancer therapies and late effects. Having a plausible set of risk factors is a necessary first step in building a clinically relevant risk prediction model. For cancers and treatments where risk factors are established, prediction models are a reasonable approach.

Predictive models of late effects may also be limited by the difficulty of extrapolating to the survivorship setting. Symptoms or conditions that may be modifiable in the general population may not be as amenable to intervention in cancer survivors. Without a full understanding of the mechanisms underlying each late effect, we cannot assume that interventions that are used in the general population will work in survivor populations. However, randomized trials of the benefit of screening and prevention among cancer survivors are difficult, if not impossible, to implement. In the absence of evidence from trials, it is reasonable to proceed with prediction models that use the best available data.

Taken together, the fourteen models in this review are of widely varying quality and utility in practice. From the perspective of study design, Alemozzafar et al. Travis et al., and Kovalchik et al. present prospective studies and trials with more than 1,000 participants from more than one institution.(8, 15, 16) The two externally validated studies (Alemozzafar et al. and Kovalchick et al.) provide the most confidence in using their models among survivors.(15, 16) However, the Alemozaffar et al. model requires a pretreatment health-related quality of life assessment that may not typically be administered in clinical practice. (15) Clinically, the long follow-up provided in models by Travis et al. and Kovalchik et al. enable intervention well after the early post-treatment years.(8, 16) These models, along with those by Romond et al. and Ezaz et al., predict late effects that can potentially be modified (heart disease) or prevented at an earlier and treatable stage (breast cancer and thyroid cancer).(17, 19) Clinicians must weigh these important factors when deciding whether to use prediction models in practice, and how much credibility to give the risk estimates found in their own patient populations.

In addition, the models in this review may form important foundations for future research. First, as noted already, more models need to be developed to address the gaps in the literature – models that use readily available data to predict serious and modifiable late effects over the long term. Second, multiple models in this review would benefit from external validation to inform clinical implementation. Third, when new risk factors are identified, their contribution to existing prediction models can be evaluated. Finally, the models can identify high-risk survivors with whom to test risk-reducing, educational, or surveillance interventions.

Our systematic review has some limitations. Our search strategy may not have captured all existing papers, particularly those that did not explicitly refer to risk prediction or the term “late effect” in the title or abstract of the paper. Conversely, because some papers present

absolute risks without describing them as such, reviewers may have missed these less salient models. Our decision to include only models predicting late effects that are present one year after treatment completion may have excluded models that clinicians and survivors would value. Similarly, our decision to exclude models that require dosimetry data may have eliminated models from our review that could benefit radiation oncologists following patients after treatment completion. However, our focus was applicability to clinicians in the survivorship setting who did not prescribe treatment, and we believe our criteria were appropriate for this purpose.

In conclusion, our systematic review identified fourteen models predicting late effects among cancer survivors. Few models address modifiable and serious late effects, limiting their utility for risk stratification. Considering the large number of late effects that are appropriate for modeling and for which risk factors are known, cancer survivors would benefit from the development of models explicitly focused on long-term, modifiable, serious late effects. Such models may inform the management of survivorship care, either by risk-stratifying interventions in the oncology setting or by establishing the appropriate balance of oncology and primary care after treatment completion. The output of prediction models could be disseminated to survivors as part of their survivorship care plans, providing much-needed tailored information to guide ongoing survivorship care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We searched for all statistical models that satisfied two criteria: (1) they predict the absolute risk of late effects and (2) they could be used in a clinical setting to guide the care of cancer survivors.
- We identified 14 published studies that modeled 9 distinct late effects.
- Only 2 studies externally validated their prediction models. Clinical prediction models rarely predicted severe, modifiable late effects that appear after an asymptomatic period.

Figure 1.
PRISMA diagram of article selection

Table 1

Study Characteristics

Study details		Development			Model	
First Author (Year)	Late Effect(s)	Timing of Latest Prediction	Sample Description	Sample Size (Late Effect Prevalence)	Inputs	Validation (Type of Output)
Prostate cancer						
Alemozaffar (2011)	Erectile Dysfunction	2 years	Multicenter US cohort study. Patients had stage T1 or T2 and either: 1. Prostatectomy 2. Radiation Therapy 3. Brachytherapy	1,027 overall (63%) 524 (65%) 241 (63%) 262 (57%)	Age Body mass index Pretreatment PSA Pretreatment sexual health Race/ ethnicity	External (Predicted probabilities table)
Briganti (2010)	Erectile Dysfunction	3 years	Retrospective single-institution Italian cohort. Patients had nerve sparing surgery, no adjuvant treatment, and either: 1. No erectile dysfunction treatment 2. Erectile dysfunction treatment	435 overall (42%) 193 222	Age Comorbidity Pretreatment sexual health	Internal (Risk classification scheme with graph)
Gallina (2008)	Erectile Dysfunction	3 years	Single-institution prospective Italian cohort. Patients had nerve sparing surgery.	268 (Not available)	Age at prostatectomy Posttreatment therapy Pretreatment sexual health	Internal (Nomogram)
Kilminster (2011)	Erectile Dysfunction	4 years	Meta-analysis of 33 studies of pre- and postoperative erectile function. Type of surgery: 1. Open 2. Laparoscopic 3. Robotic	6,653 (26–51%) 2,466 (26–42%) 3,420 (0–40%)	Age at surgery Time since surgery	None (Nomogram)
Eastham (2008)	1. Erectile Dysfunction 2. Biochemical Recurrence 3. Urinary Incontinence	2 years	Single-institution prospective US cohort. Patients had T1c to T3a disease, treated with radical prostatectomy	1,577 (38%)	Age at surgery Biopsy grade Months since surgery Pretreatment PSA Pretreatment sexual health Stage	Internal (Nomogram)

First Author (Year)	Study details		Development		Model	
	Late Effect(s)	Timing of Latest Prediction	Sample Description	Sample Size (Late Effect Prevalence)	Inputs	Validation (Type of Output)
Mathieu (2013)	Urinary Dysfunction	5 years	Multicenter prospective and retrospective French data. Patients had definitive radiotherapy.	965 (19%)	Anticoagulation Radiation dose	Internal (Nomogram)
Chipman (2014)	Sexual Dysfunction	2 years	Multicenter prospective US cohort. Patients had stage T1 or T2 disease and radical prostatectomy.	493 (Not available)	Age Pretreatment health-related quality of life Pretreatment PSA Surgical technique	Internal (Predicted probabilities table)
Breast cancer						
Bevilacqua (2012)	Arm Lymphedema	5 years	Single-institution prospective Brazilian cohort study. Patients had conservative surgery with axillary lymph node dissection.	1,054 (23%)	Age Body mass index Chemotherapy cycles Early edema Level of axial node dissection Radiation field Seroma	Internal (Nomogram)
Ezaz (2014)	Heart Failure or Cardiomyopathy	3 years	SEER-Medicare database. Patients had stage III, HER-2+ disease, treated with surgery and trastuzumab.	832 (19%)	Age Cardiovascular risk factors Chemotherapy	Internal (Risk score and table)
Ganz (1993)	Psychosocial Morbidity	1 year	Multicenter randomized trial in US. Participants had stage I or II disease, surgery, no history of major psychiatric illness.	227 (14–44%, based on risk)	Age Functional status Posttreatment cancer-specific quality of life	Internal (Decision tree)
Romond (2012)	Cardiac Event	5 years	Multicenter randomized trial in US. Patients had node positive, HER2+, nonmetastatic disease, treated with surgery/axillary dissection, anthracyclines, and trastuzumab.	944 (4%)	Age Baseline left ventricular ejection fraction	Internal (Equation and graph)
Head and Neck Cancer						
Langendijk (2009)	Swallowing Dysfunction	6 months	Single-institution, prospective Dutch cohort study. Patients treated with radiotherapy and were disease free after 6 months.	529 (23%)	Accelerated radiotherapy Bilateral irradiation Concomitant chemoradiation Primary tumor site Stage Weight loss	None (Risk score and graph)
Hodgkin Lymphoma						

First Author (Year)	Study details		Development		Inputs	Model Validation (Type of Output)
	Late Effect(s)	Timing of Latest Prediction	Sample Description	Sample Size (Late Effect Prevalence)		
Travis (2005)	Breast Cancer	30 years	International population-based cohort. Patients diagnosed at age 30.	3,817 (3%)	Age at diagnosis Alkylating agents Mediastinal radiation dose Time since treatment	Internal (Predicted probabilities table)
Childhood Cancer						
Kovalchik (2013)	Thyroid Cancer	20 years	International population-based cohort study and two French nested case- control studies. Patients treated with radiation to thyroid.	12,150 (1%)	Age at diagnosis Alkylating agent Birth year Initial cancer type Past thyroid nodule Radiation Radiation to neck Sex	External (Calculator)