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► **To cite this version:**

Charlotte Demoor-Goldschmidt, Florent de Vathaire. Review of risk factors of secondary cancers among cancer survivors. *British Journal of Radiology*, 2018, pp.20180390. <10.1259/bjr.20180390>. <hal-04410527>

HAL Id: hal-04410527

<https://hal.science/hal-04410527v1>

Submitted on 22 Jan 2024

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HAL Authorization

Received:
02 May 2018

Revised:
10 July 2018

Accepted:
07 August 2018

<https://doi.org/10.1259/bjr.20180390>

Cite this article as:

Demoor-Goldschmidt C, de Vathaire F. Review of risk factors of secondary cancers among cancer survivors. *Br J Radiol* 2019; **92**: 20180390.

REVIEW ARTICLE

Review of risk factors of secondary cancers among cancer survivors

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ABSTRACT

Improvements in cancer survival have made the long-term risks from treatments more important, in particular among the children, adolescents and young adults who are more at risk particularly due to a longer life expectancy and a higher sensitivity to treatments. Subsequent malignancies in cancer survivors now constitute 15 to 20% of all cancer diagnoses in the cancer registries. Lots of studies are published to determine risk factors, with some controversial findings. Just data from large cohorts with detailed information on individual treatments and verification of what is called "secondary cancers" can add some knowledge, because their main difficulty is that the number of events for most second cancer sites are low, which impact the statistical results. In this review of the literature, we distinguish second and secondary cancers and discuss the factors contributing to this increased risk of secondary cancers. The article concludes with a summary of current surveillance and screening recommendations.

RATIONALE

Statistics reporting from the different cancer societies show the death rate from cancer has declined steadily over the past two decades. The substantial progress reflects both improvements in treatments and earlier diagnosis. This has led to a greater importance of potential long-term sequelae.

Second cancers now constitute 15 to 20% of all cancer diagnoses in the cancer registries.

Among paediatric patients, modern radiotherapy techniques, combined with new chemotherapies, have contributed significantly to an improvement in survival rates, with current 5-year cure rates above 80% for the child or Hodgkin lymphoma (HL).¹⁻³ Nevertheless, 40 to 70% of former patients will present with a health problem related to the disease or the treatment.⁴⁻⁷ The risk of a second cancer is significantly higher than in the general population, between 3- and 10-fold.⁸⁻¹⁰ For solid cancers, standardised incidence ratios (SIRs), which is the ratio of observed and expected number of second cancers, decreased with increasing age at the time of the diagnosis of the childhood cancer and decreased with higher time since diagnosis, whereas excess absolute risk, defined as observed minus expected number of second cancers, increased with higher

follow-up time.⁹ For haematological malignancies, SIR and excess absolute risk peaked 5 to 9 years since diagnosis and fell down afterward.

Among these other cancers occurring over time, the second cancers are distinguished from the so-called secondary cancers with a share of iatrogenicity because of being related to the treatments received. An iatrogenic secondary tumour risk was observed both after radiotherapy (radiation-induced cancers) and after chemotherapy. Having a first cancer does not protect, or "vaccinate", against a second. Then, the same causes producing the same effects, the persistence of certain lifestyle behaviours and/or environmental conditions can obviously increase the risk of a second cancer in a cancer patient compared to the general population. For example, it is known that tobacco intoxication is linked with a higher risk of several cancers [e.g. pulmonary, head and neck (ORL), bladder and oesophagus]. Moreover, we know better and better the role of genetics. Without even being in groups of high-risk patients (like those with BRCA 1 and 2 mutations for breast cancers) or at very high risk of multiple cancers (like those with Li-Fraumeni syndrome), it seems likely that because of their genetic heritage, some patients are more at risk to develop a second cancer than the general population.

Also, the risk of second cancer depends on several factors, such as personal medical history and treatments of the first cancer, immunosuppression, age, hormonal and environmental influences, genetic predisposition and infection. Treatment-related risk factors have been well-studied among childhood cancer survivors, but most of these studies don't take into account the environmental exposures and lifestyle during their adulthood. Several factors can explain the bigger impact of treatments on increased risk of secondary cancers among children than for adults: a higher sensitivity to ionizing treatments, a higher rate of genetic susceptibility, the longer time of follow-up and just simply because a higher impact of a radiation field because of the difference in body size.

Lots of studies are published to determine risk factors, with some controversial findings. Just data from large cohorts with detailed information on individual treatments and verification of what is called "second cancers" can add some knowledge, because their main difficulty is that the number of events for most second cancer sites are low, which impact the statistical results. All these studies must be interpreted with caution when the elevated overall risk is not paralleled by clear dose-response patterns and when results are not supported by other epidemiological studies.

In this review of the literature, we discuss the factors contributing to this increased risk of secondary cancers and conclude with a summary of current surveillance and screening recommendations.

RISK FACTORS

Chemotherapy

Several chemotherapeutic agents are known to increase the risk of leukaemia, with a short delay after the chemotherapy.

Alkylating agents – median time after treatment 4–6 years: In the Childhood Cancer Survivor Study (CCSS), which is a retrospective cohort of children and adolescents treated in one of the 26 participating institutions in the United States and Canada between January 1970 and December 1986 and surviving at least 5 years after diagnosis, alkylating agents were found as significant risk factors with a relative risk (RR) of 1.4–2.2. It concerned mainly acute myeloid leukaemia (AML), with specific cytogenetic characteristics (monosomy or partial deletion of chromosomes 5 and 7).^{11,12} The epipodophyllotoxins used alone or in combination with alkylating agents increased the risk, linearly with the dose but not with the modality and the treatment regimen.^{13,14} In a French case control study (61 cases, 196 controls), patients who received between 1.2 g m⁻² and 6 g m⁻² of epipodophyllotoxins or >170 mg m⁻² of anthracyclines had a 7-fold higher risk [95% confidence interval (CI), 2.6 to 19]. In this study, exposure to alkylating agents or radiotherapy did not increase the risk.¹⁵ This was also observed among adult cancer survivors.^{16,17} Other specific abnormalities have been described, as for example after anthracycline treatment t (8; 21)(p11; p13.3).¹⁸

Topoisomerases – median time after treatment 1–3 years. These molecules increased the risk of myeloid leukaemia, mainly AML4 and AML5 with frequent translocation involving the MLL gene

(balanced translocations involving chromosome bands 11q23 and 21q22).^{16,18} This risk depended more on the administration modality (higher risk if administered intermittently) than on the cumulative dose and increases 4-fold after a 4000 mg m² etoposide dose.¹⁹

More recently, some studies have found an impact of chemotherapy on the risk of second solid cancer. For example in two big cohorts, the CCSS and the Dutch cohort, an exposition to anthracyclines (cumulative dose >250 mg m⁻²) among patients without radiotherapy, significantly increased the risk in link with the cumulative dose, respectively, with an SIR = 3.8 (1.7–8.3) and hazard ratio = 3.1 (1.4–6.5).^{10,20}

Radiotherapy

Radiation-induced cancers have been known since the dawn of radiation therapy, but it is just since the end of the 20th century that radiotherapy oncologists had modern tools to limit the irradiation of healthy tissue, as imaging tools, computerized treatments planning systems, new radiation machines leading in new radiation techniques. This progress led to the possibility of providing escalating radiation doses to the tumour while sparing the healthy surrounding tissues. Despite important and recent advances in radiotherapy, the risk of second cancers arising in long-term survivors continues to be a problem. They represent only a small percentage (less than 10%) of cancers occurring secondarily after radiotherapy in adulthood; the vast majority of these "second cancers" are related to genetics or lifestyle, for example, a second cancer in the ORL field occurring 2 or 3 years after a first ORL or the superior part of the oesophagus in a patient who has continued to drink alcohol. But this scarcity must in no way make them ignore or obscure that the latency of development of post-irradiation secondary cancer is bigger than after chemotherapy and is in the order of 10–15 years after the first treatment.²¹

Therefore, there was a need to develop risk assessments based on knowledge of radiation-induced carcinogenesis. This leads in improvement of treatment regimens. Many factors related to the radiation treatment modify the risk and are developed below.

Age and dose

One of the major studies available in this field was published in 2011 by Berrington and Gonzalez.²² It involved 647,672 cancer patients (oral and pharynx/salivary gland/rectum/anus/larynx/lung/soft tissue/female breast/cervix/endometrial/prostate/testes/ eye and orbit/brain and CNS/thyroid cancer) with an average follow-up of 12 years treated from 1973 to 2002. The age of the patients was 20 years or older. Of these, 60,271 (9%) developed a second solid cancer. RRs for second cancers in patients treated with radiotherapy vs patients not treated with radiotherapy were estimated with Poisson regression adjusted for age at diagnosis, attained age, stage, gender and year of diagnosis. Only a small part of these second cancers (8%) (95% CI, 7–9%) could be related to radiotherapy, meaning 5 excess cancers per 1000 patients treated with radiotherapy by 15 years after diagnosis. The relative risk increased with younger age at treatment, larger treatment fields, time since diagnosis and decreased with

increasing age at diagnosis. Moreover, higher attributable risks were most likely for organs located inside the fields.

In a recent review of the literature after breast cancer, in which results of 22 studies were included, comprising 245,575 irradiated and 277,164 non-irradiated females, a significant risk of second cancer was observed for both groups [SIR of 1.23 (1.12–1.36) and SIR of 1.08 (1.03–1.13), respectively]²³ (*i.e.* about 15% of second cancers were attributable to radiotherapy). The localisation of the second breast cancer and the risk over time were different: lung, oesophagus, thyroid and connective tissue (sarcoma) for irradiated females, with a significant risk over time; and for non-irradiated females, thyroid and sarcomas, with a significant risk just in the 10 after breast cancer.

Further research is needed to evaluate the impact of radiotherapy among adult cancer survivors on secondary cancers with newer radiotherapy techniques, such as intensity-modulated radiation therapy, proton therapy and efforts to reduce treatment doses and volumes.

Focusing on childhood cancer survivors who have greater risks, irradiation was the strongest independent factor and was associated with an RR of developing a secondary cancer of 2.7 (95% CI, 2.2–3.3)^{9,24} in the CCSS. Similarly, in a case-control study of the German Childhood Cancer Registry involving 328 secondary childhood cancer cases *vs* 639 controls, radiotherapy was associated with an odds ratio (OR) of 2.05 (95% CI, 1.45–2.91) of developing cancer, even after adjustment according to different chemotherapies, but the follow-up was short.²⁵ In currently published studies, secondary tumours more frequently described after radiotherapy in childhood are benign (meningioma) or malignant with frequency of skin, breast, thyroid, bone and soft tissue cancers (sarcomas). But in the future ones, when survivors will be older, radiation-induced adult type carcinomas, such as lung or digestive cancers, will be increasingly more frequent.

For example, the risk of secondary breast cancer increases with the dose of radiotherapy received on the mammary bud, a large dose/session, a wide radiation field, a young age (progressive decrease after puberty to become insignificant after 30 years), a radiotherapy treatment nearby (1 month) or during pregnancy, a conserved hormonal status, a history of HL and a history of breast cancer in a first-degree relative.^{26,27} In the CCSS cohort, among the 1230 female survivors exposed to chest radiotherapy, the cumulative incidence of breast cancer was 30% by age 50, or a cumulative incidence of 35% among the survivors of HL, which is comparable to that of BRCA mutation carriers in the general population.^{28–32} The risk of developing secondary sarcoma increases with the dose received by the organ, and the risk is 30-fold higher after 44 Gy than 14 Gy.^{33–36} In the CCSS case-control study, radiotherapy is a risk factor for secondary sarcoma with an OR of 15.6 (95% CI, 4.5–53.9) for 10–29.9 Gy, which increases to 114.1 (95% CI, 13.5–964.8) for doses >50 Gy.³⁶ Sarcomas were also described after Ewing sarcomas, often cured with a relative high dose (50–55 Gy).^{37–39} Survivors of paediatric cancers are also at risk for digestive cancers, especially colonic in the case of treatment with abdominal radiotherapy [RR 11.2 (7.6–16.4)]. In

the CCSS in a multivariate analysis, procarbazine with a cumulative dose >7036 mg/m² and platinum were found as significant risk factors.⁴⁰ A study done at St. Jude Hospital found the same results with a significant impact of alkylating agents.⁴¹ There was also an increased risk of stomach cancer when the field included this organ.⁴² The risk of cutaneous cancers excluding melanomas, mainly basal cell carcinomas, was increased in patients who have had radiation therapy.⁴³ In a CCSS case-control study, survivors who received 35 Gy or more to the skin were at a significantly increased risk with an OR of 39.8 (8.6–185). For those with full body irradiation and allografts, the risk increased with young age and if there had been a reaction (acute or chronic) of graft versus host disease.⁴⁴ In the CCSS, authors found a significant risk with small dose exposure, from 1 Gy, and increasing with the dose [1–4.9 Gy, RR = 3.6 (1.4–9.1); 5–14.9 Gy, RR = 11.7 (4.9–27.9); 15–24.9 Gy, RR = 14.9 (6.0–37.3); 25–34.9 Gy, RR = 22.2 (7.5–65.8); 35–63.3 Gy, RR = 39.8 (8.6–185)]. In multivariate analysis, persons with pale skin or blond hair, or strawberry blond or red hair, had no significantly increased risk compared to persons with brown or black hair.⁴⁴ In early years, brain tumours were associated with prophylactic craniospinal irradiation used to treat patients for acute lymphoblastic leukaemia. Still in the CCSS, the risk of glioma and meningioma depended on the dose of radiation [OR 6.8 (1.5–29.7) and 9.9 (2.2–45.6), respectively], and for glioma, mainly children treated under the age of 5 years.⁴⁵

Size of the field

The risk of secondary cancers increased with increasing radiation field size.⁴⁶ For example, for patients treated for HL compared with the age-matched and sex-matched general population, the relative risk for patients treated with mantle radiation alone was 2.1 *vs* 4.2 and 5.1, respectively, for the ones treated with subtotal and total lymph node irradiation.⁴⁷ Concerning the specific risk of breast cancer among these survivors, in a cohort of 1112 female 5-year survivors treated before the age of 41 years, full mantle irradiation increased the risk 2.7-fold compared with mediastinal irradiation alone [hazard ratio, 2.7 (1.1–6.9)].⁴⁸ All breast cancers occurred within the initial radiation fields.

Organ sensitivity

The sensitivity to radiation varies with the irradiated organs. Berrington and Gonzalez reviewed epidemiological studies that assessed the dose-response relationship for second cancers occurring after fractionated treatments of radiotherapy.⁴⁹ A linear dose-response curve was most of the time observed, except for thyroid cancer, for which there was a plateau and then a decrease in risk noted at doses received by the thyroid >20 Gy.^{33,50–54} In the French Childhood Cancer Survivor Study, de Vathaire et al found the same curve regarding the risk of renal cancer with an increasing risk until 20 Gy, and the risk decreased at larger doses.⁵⁵

Environmental influence

Breast cancer among HL survivors has been well-described, but lung cancer is also a major concern given recent growing evidence for and interest in radiation-induced lung cancers. A study by Gilbert et al matched 227 HL survivors who developed a

second lung cancer with 455 HL survivors without lung cancer.⁵⁶ They found that the estimated excess relative risk per Gy was 0.15 (0.06–0.39), and that the effects of radio- and chemotherapy were additive, whereas the effects of radiation and smoking seemed to be multiplicative.

Hormonal influence

Early menopause was associated with a lower RR for breast cancer after radiation, which decreases breast tissue exposure to hormones. A treatment with alkylating chemotherapy was found also to decrease the RR, probably because many patients have early menopause afterwards.^{31,57–59} This is also observed when the ovaries were included in the field of the radiation treatment.^{31,60,61}

Another example for the importance of hormonal influence is after a long treatment using tamoxifen.⁶² This molecule is used to treat breast cancer with hormonal receptors for non-menopausal females but it has been well-described that this treatment increases the risk of endometrial cancer. (OR = 1.52; 95% CI = 1.07–2.17). The risk of developing endometrial cancer increases with the duration of tamoxifen treatment [particularly when used more than 5 years, OR = 4.06 (95% CI = 1.74–9.47)] than non-users.⁶³

CHEMOTHERAPY AND RADIOTHERAPY

Some specific agents have been described to increase the risk of second solid cancers after adjustment with radiotherapy treatment, principally alkylating agents and anthracyclines with an increasing risk with the cumulative dose (e.g. breast,²⁰ sarcoma,^{64–66} lung,¹² stomach⁶⁷ and pancreas⁶⁸). In the CCSS, including 12,756 patients to study second thyroid cancer, for patients treated with small doses of radiotherapy (<20 Gy received by the thyroid), treatment with alkylating agents increased thyroid cancer risk with an RR of 2.4 (1.3–4.5) and treatment with anthracyclines with an RR of 1.8 (1.1–3.1). The risk was not significant for patients not treated with radiotherapy or for whom the dose was >20 Gy.²⁶ In another study done on 4438 patients of the French Childhood Cancer Survivor Study, de Vathaire et al, showed that nitrosoureas (BCNU or CCNU), classified as alkylating agents, increased the risk of second thyroid cancer 6.6 (95% CI, 2.5–15.7).⁵⁰ Alkylating agents were also described as risk factors for second digestive cancers among childhood cancer survivors.^{40,41}

CONCLUSION

It is important to identify and determine the risk of second tumours for cancer survivors, taking into account the different treatments, such as chemotherapy, radiotherapy and hormone therapy. It is difficult to conclude a strong risk of chemotherapy-induced solid cancers when reading all the articles on this subject, but agents, such as alkylating drugs, seem to play a role and to modulate the risk. Histological features or better specific signatures are needed to better classify and give a proof that it is really secondary cancers.^{28,69–73} Additional research is needed to better understand the role of specific chemotherapeutic agents, individually, in combination, in combination with radiotherapy

and in combination with environmental exposure. Moreover, data are needed about new classes of anticancer agents. With regard to radiotherapy, the main factors to take into account are the age of the patients, the sensitivity of the organs and the dose received by these organs.^{74–76}

In the future, physicians will also have to consider chemotherapy exposure, genetic susceptibility and environmental exposure, which modify the risks when determining the indications for cancer surveillance in cancer survivors. They will also take profit of the availability of Dicom Radiotherapy data, which will permit precise knowledge of radiation dose distributions in body organs and, therefore, a better anticipation of iatrogenic risks. The genomic approaches and predisposition was well-described for secondary AML and research is ongoing for solid cancers.^{77–80}

Several guidelines are published and recommend screening programmes.^{74,81–83} The most well-defined and harmonised by the International Late Effects of Childhood Cancer Guideline Harmonisation Group is breast cancer screening based on annual MRI, after an interval of 8 years with the radiation treatment and beginning at the age of 25 years old (or after, depending on the age at the time of radiotherapy) when part or all of the mammary tissue has received 10 Gy (moderate recommendation) or more (>20 Gy, strong recommendation).⁸⁴ Some national programmes are ongoing to help follow these recommendations.³⁰ For the thyroid, the exact screening is discussed because of the small speed of development. Most of the recommendations agree with ultrasound screening every 2 to 5 years. Some just recommend clinical examinations.^{85–87} Regarding the risk of cutaneous cancer and melanoma, the National Cancer Institute and Children's Oncology Group guidelines, as well as other national guidelines (SFCE, French Society of Childhood Cancer), emphasise the importance of annual clinical examination for skin cancer screening. However, the literature reports that less than one-third of survivors of paediatric cancer have ever had a clinical skin examination by a physician.^{75,88,89} In addition, the Children's Oncology Group recommends for survivors who were exposed to more than 30 Gy for an abdominal field to undergo colonoscopy at a minimum of every 5 years beginning at 10 years after radiation or at age 35.

In conclusion, because of great advances in treatment options, cancer survival rates are improving and long-term follow-up strategies become more and more important. The goal and the graal in research into cancer aims to better understand, prevent and treat late-occurring effects while preserving and still increasing the rates of long-term survival. A summary of treatments with detailed recommendations of screening and advice for lifestyle is necessary for each cancer survivor, especially for each child and adult treated with radiotherapy in order to better organise its follow-up in the long term. Second cancers are multifactorial, with key roles played by primary cancer treatments and genetic susceptibility without forgetting lifestyle factors and environmental exposures. To remember, less than 10% of second cancers occurring among adult cancer survivors can be attributed to radiotherapy.

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