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A review of health behaviours in childhood and adolescent cancer survivors: towards prevention of second primary cancer

Abstract

Survival of children, adolescents and young adults treated for cancer has increased with improved treatments. But there is still an increased risk of second primary cancer (SPC) in the long term compared to the population of the same age, especially related to treatments. The follow-up of this population and the prevention of SPC are important issues. Therefore we aim to review the available literature on cancer risk factors (lifestyle and occupational exposures) in children and AYAs previously treated for cancer, to identify interventions that might be implemented to improve healthy behaviors in this population.

We searched PubMed using the following terms: "cancer[Tiab] AND young adult[Tiab] or teen[Tiab]or childhood[Tiab] AND prevention[Tiab] AND survivors[Meshterm]''.

Twenty-seven articles were included. Children, adolescents and young adult survivors of cancer have similar risk behaviors to their peers regarding tobacco, diet and sun exposure; however, they have lower physical activity. We identified few studies on prevention strategies in this population. Results of available studies remain inconclusive. No publications were found on occupational exposure and risk of second cancer.

Children, adolescents and young adults treated for cancer are a population at risk and require specific effective prevention strategies.

Keywords: second malignancy; prevention; childhood; risk factors; survivors

Introduction

Survival rates for children and adolescents with cancer have improved due to new treatments. All cancer, 5-year survival rates are around 80%.[1] Alongside these improvements the long-term consequences of the disease and its treatment are substantial. Cancer treatments in children and adolescents lead to long term adverse effects including endocrine dysfunction, cardiovascular disease, metabolic syndromes, decreased fertility and impaired quality of live. Radiotherapy and chemotherapy significantly increase the risk of second malignancies.[1,2] The latter represent the most common cause of treatment-related death in long-term survivors of childhood cancer.[1] Cancers in children, adolescents and young adults represent a heterogeneous group of disease that vary widely in incidence, age at diagnosis, type of treatment, survival and most probably etiology.[3] The definition of age limits for adolescents and young adults (AYAs) in the literature varies widely across studies, publication periods and countries. While most authors consider 15 years as the lower boundary, the upper age cutoffs ranges from 24 to 29, or sometimes 39 years.[4] Survivors of cancer aged below 17 years at initial diagnosis are 6 times likelier to develop a second cancer compared to the general population of the same age.[3] This risk is 2 to 3 times that for people treated for cancer aged 18 to 39 years at initial diagnosis.[3] The cumulative incidence of second malignancies in the Childhood Cancer Survivor Study (CCSS) at 30 years after initial cancer diagnosis was 21% for all subsequent neoplasms, 9 % for non-melanoma skin cancer, and 11% for second malignant neoplasms (excluding non-melanoma skin cancer). Excess risk was observed for all primary cancer localisations. The ten most frequent second malignant neoplasms (excluding non-melanoma skin cancer) observed in the CCSS (median follow-up of 23 years), were breast cancers (23%), thyroid cancers (15%), Central Nervous System (CNS) tumours (10%), soft tissue sarcomas (9%), melanomas (6%), bone cancers (6%), head and neck cancers (5 %), osteosarcomas (4 %), lymphomas (4%), small intestine and colorectal cancers (3%), with a mean age of 29.5 years at subsequent neoplasm diagnosis. A significantly increased incidence with two to thirtyfold standardized incidence ratio (SIR) was observed for all localisations compared to the general population including three to tenfold SIR for cancers that are more typical of cancers in older adults, such as breast cancer, small intestine cancer, head and neck cancer, CNS tumours, lung cancer, and leukaemia.[5]

Female sex, older age at diagnosis, earlier treatment era, and radiation therapy were associated with increased risk of subsequent neoplasms. Differential exposure to cancer risk factors, such as lifestyle (tobacco, diet, physical activity) may also be associated with increased risk of second malignancies, but has been poorly studied in AYAs. To improve the prevention of second malignancies, we searched the available literature on cancer risk factors (lifestyle and occupational exposures) in

children and AYAs previously treated for cancer. Our article also reviewed the interventions that can be implemented to improve healthy behaviours in this population. We focused our study on cancer risk factors known to be associated with the cancer types having shown an increased incidence in children and AYAs previously treated with cancer: smoking (lung cancer, breast cancer, colorectal cancer, leukaemia),[6] diet, nutrition and physical activity (colon cancer, rectal cancer, breast cancer, skin),[7] sun exposure (skin cancer), alcohol (breast cancer, colorectal cancer), and occupational exposures (lung cancer, leukaemia, skin cancer, bone sarcomas, CNS tumours).[8,9]

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Methods

We searched PubMed until June 2014, with no restriction on the earliest date of the publications, using the terms 'cancer [tiab] AND young adult [tiab] or adolescent [tiab] or childhood [tiab] AND prevention [tiab] AND survivors [mesh term]', and limited to articles in English and French. The search was completed using online data from the Public Health data bank, International Agency for Research on Cancer (IARC) website, and various websites (sanitary, occupational and environmental agencies) and consensus conferences. We also searched the reference lists of related articles.

The articles (epidemiological studies, intervention studies and literature reviews) were selected on their summary and further through the full article. We selected articles dealing with the risk of second malignancies associated with life style factors or occupational exposures as well as articles on cancer prevention strategies for the malignancies seen as second cancers after childhood and AYA cancer. To take into account the substantial variability in the age ranges used by authors across studies, and facilitate the analyses of available publications, we did not apply a predefined age range for this population. Articles dealing with 2nd cancers related to genetic predisposition or psychosocial consequences of second malignancies, screening and surveillance practices were not included. We also excluded articles dealing specifically with the risk of second malignancies associated with treatment of a first cancer as extensive reviews of the literature have been published previously on this topic.[2,5]

Results

Of the 105 articles identified by our search, we included 27 articles of which 14 dealt with behavioural risk factors and 13 with health promotion including preventing risk factors for second

cancers. See Figure 1. Flow diagram for the search. Fifty seven articles were excluded after reviewing the full publication because they did not match our eligibility criteria. Fifteen of the articles were unavailable through our library or interlibrary services within the review time scope. Fifteen of the articles were excluded after full reviewing by two reviewers (JC, SD) considering them outside the scope. Table 1 provides a detailed description of the main studies included in our search (see Table 1).

Behavioural factors

Overall, 14 publications addressed lifestyle factors, such as smoking, cannabis use, alcohol consumption, sun exposure, physical activity and nutrition. Four focused especially on AYAs previously treated for cancer.[10-13] Three articles focused exclusively on smoking,[14-16] and six on physical activity and nutrition.[17-22] One publication dealt with sun exposure in AYAs who had previously been treated for cancer.[23]

Tobacco

Overall, five studies focused on smoking in young cancer survivors.[11,12,14-16] Smoking prevalence in survivors varied between 10 and 29%. Two studies found significantly lower prevalence of smoking in survivors of AYA cancers compared to the general AYA population.[11,12]

Kahalley et al. studied factors associated with smoking in 307 adolescents from the CCSS.[14] In this study, the percentages of current smokers (10%) and past adolescent smokers (28%) were similar to those in the general population (9 and 33% respectively). Factors associated with increased prevalence of recent smoking (having smoked in the week before the survey) were eating disorders (bulimia, anorexia), psychiatric problems (e.g. suicidal behavior), emotional distress, having friends who smoke and having smokers in their household. Tyc et al. studied the factors associated with starting smoking in 94 preadolescents with cancer and in 190 preadolescents without cancer.[15] In this study, no preadolescents with cancer and only 0.5% of preadolescents without cancer reported current smoking (a non-significant difference). Preadolescents without cancer were more likely to report future intent to smoke compared to preadolescents with cancer (34.1% vs 14%; $p < 0.001$). They were also more likely to have a close friend who smoked (16.8 vs 7.5%, p=0.03). Preadolescents

with cancer had a better knowledge of the risks related to tobacco smoking in general (p=0.001) and of their own specific risks (p < 0.001). They attributed more value to overall health (p=0.001). Intent to smoke was significantly associated with age, gender (male being at greater risk), the absence of cancer, having parents or friends who smoke and perceived vulnerability to tobacco-related illnesses.[15]

Regarding cannabis smoking, an Australian study showed that cannabis use was significantly lower among the 153 adolescents treated for cancer than in the age-matched healthy population.[11]

Tercyak et al. evaluated the prevalence of three behavioural risk factors (smoking, insufficient physical activity and non-compliance with recommendations on sun exposure) in adolescents aged 11 to 22 years who had had childhood cancer. Regarding smoking, 50 % of the participants smoked, whereas 53 % declared not having any of these risk behaviours, 28 % declared one of the three risk behaviours, 12% having two of the three risk behaviours, and 7% having all three (see details in Table 1).[13]

Alcohol

Two studies showed significantly lower alcohol consumption among childhood or adolescent cancer survivors compared to the age-matched healthy population.[11,12] Compared to their healthy peers, younger survivors (13 to 17-years) less frequently reported alcohol use (OR=0.44, 95% CI: 0.39-0.49); whereas older adolescent survivors (18 to 24-years) more frequently reported alcohol use (OR=1.5, 95% CI: 1.0-2.2).[11] See Table 1.

Overweight, obesity

Seven studies investigated factors associated with unhealthy lifestyle, overweight and obesity in people who had had cancer as children, adolescents or young adults. Three studies reported a relationship between obesity and cancer treatment.[20,21,24] Children with acute lymphoblastic leukaemia who received a dose of radiotherapy to the brain greater than 20 Grays (Gy) before the age of four had a four-fold increased risk of obesity; this was especially true for women.[24] The risk of obesity in women treated for a brain tumour was higher if they were less than 4-years old at diagnosis.[20] A review of the literature reported a low rate of physical activity, little motivation to undertake sports and difficulties meeting nutritional recommendations among childhood cancer survivors.[18] However the proportion was similar to the healthy age-matched population with

adolescents having a less healthy lifestyle in general (eating at fast-foods, decreased physical activity).[22]

Sun exposure

Buchanan et al. studied sun exposure in 9298 survivors of childhood cancer, diagnosed prior to 21 years of age, from the CCSS cohort. Compared to the 2950 matched controls (who were siblings of the cases), cancer survivors exposed themselves significantly less to the sun, used significantly less artificial tanning devices and had used more sunscreen the previous summer.[23]

Results from Tercyak et al.'s study showed that 37% of the participants didn't follow recommendations on sun exposure. Among the 28 % of participants reporting only one risk behaviour, non-compliance with recommendations on sun exposure was the most common (17%).[13] See Table 1.

Determinants of behavioural risk factors

Overall five studies investigated factors associated with increased prevalence of behavioural risk factors. Emmons et al. studied the factors associated with starting or quitting smoking in 9709 subjects from the CCSS.[16] Factors associated with a reduced likelihood of smoking were younger age at diagnosis (< 10 years old), history of brain radiotherapy and pulmonary-related cancer treatment. Factors associated with an increased likelihood of smoking were lower education level (below bachelor level), lower annual income (< 20 000 US dollars), and not having black skin colour. Furthermore, lower education level, male gender, lesser satisfaction with life and stressful events were associated with excessive alcohol consumption in AYA cancer survivors.[12] Green et al. analysed the factors associated with obesity in 9284 adults (>18 years old) from the CCSS. Age at diagnosis (between 5 and 9 years), radiation dose to the hypothalamus and the pituitary (between 20 and 30 Gy) were significantly associated with obesity. Meeting US Center for Disease Control and Prevention guidelines on vigorous physical activity and a medium amount of cancer-related anxiety were significantly associated with a decreased risk of obesity. Use of paroxetine was significantly associated with an increased risk of obesity, compared with other drugs (see Table 1).[17] Buchanan et al. found that factors associated with regular sunscreen use in the past summer in survivors of childhood cancer were female gender, having fair skin, having previously been screened for skin cancer, and being prone to sunburn (see Table 1).[23] Older age and stress were significantly associated

with the presence of more than one risk behaviours (smoking, insufficient physical activity and non-compliance with recommendations on sun exposure) in Tercyak et al.'s study.[13]

Occupational exposures

Charbotel et al. have recently reviewed occupational carcinogenic agents associated with rare tumours, including the most frequent tumours is children and AYAs.[9] However, our search did not find any study in the literature investigating the risk of relapse or the risk of second malignancies associated with occupational exposures.

Prevention strategies to reduce unhealthy behaviours in childhood and adolescent cancer survivors

Five articles addressed the problem of prevention of 2nd cancers associated with avoidable risk factors, such as smoking, obesity and lack of physical activity in children and AYAs who had had cancer.[14,15,17--19]

Smoking cessation

Several studies on smoking cessation were identified.[10,26-28;30--34] Tyc et al. compared an educational program with follow-up telephone counselling on the risks associated with smoking to standard advice on smoking in 94 pre-adolescents and adolescents who had had cancer. Participants were aged 10 to 18 and mean time from diagnosis was 6.3 years. At 12 months, participants in the intervention group had better knowledge on tobacco, had better perception of their vulnerability and were less likely to want to smoke (differences not statistically significant).[30]

A case-control study of 21 young cancer survivors and 43 controls cancer survivors (age range 13-21 years old) looked at the impact of a decision-making and risk-education intervention and showed a marginal significant reduction in smoking among smokers at 6 months after the intervention (see Table 1).[28]

We did not identify any studies on nicotine replacement therapy (NRT) in adolescents with cancer. Recent updates of recommendations propose the use of long lasting bupropion or NRT in healthy adolescents who have a high dependency on nicotine and who wish to quit smoking.[32] However,

recommending their use in children or adolescents who have had cancer seems premature in the absence of safety and efficacy data in this population.[32] Bupropion is contraindicated in people with a history of CNS tumour due to an increased risk of seizures, thereby limiting its usefulness in adult oncology populations.[31]

Smith et al. studied the benefit of NRT combined with individual or group behavioural counselling in healthy adolescents.[33] Fourteen percent had stopped smoking at week 8 but only 5% continued to be smoke free at 6 months. Moolchan et al. evaluated the efficacy of different NRTs combined with cognitive-behavioural group therapy.[34] The 3 groups included (1) active patch (21 mg), (2) active gum (2 and 4 mg) and (3) gum and placebo patch. The proportions of participants who achieved prolonged abstinence at 3 months were 17.6% in the active patch group, 6.5% in the gum group, and 2.5% in the placebo group. The difference was statistically significant between patch and placebo, but not between gum and placebo nor between patch and gum.

Killen et al. performed a randomized clinical trial in 211 healthy adolescent smokers comparing nicotine patch plus bupropion sustained release (150 mg per day) vs nicotine patch placebo. There was no significant difference between both groups but a majority of adolescents in both groups reduced their consumption to a few cigarettes per day or less and maintained this reduction over time (26-week assessment).[27] The authors explained the lack of difference by a sub-optimal dose of bupropion, usually given at 300 mg/day in adults.

Diet, weight and physical activity

Stolley et al. reviewed the descriptive and intervention studies that included survivors of childhood cancers and a measurement of diet and physical activity. They highlighted that childhood cancer survivors engaged in health-promoting activities at rates comparable to the general population. Authors pointed that the dietary research in childhood cancer survivors is methodologically weak and that behavioural interventions have mostly targeted physical activity.[18]

The clinical study of Robien et al. with adult survivors of childhood acute lymphoblastic leukemia (ALL) suggested that in general dietary intake was not consistent with dietary recommendations: 50% of the participants met minimal goals for fruit and vegetable intake, and 50% met minimal goals for dietary fat restrictions. Eighteen percent met recommendations for 30 minutes of physical activity, 5 days/week.[19] In the multicentric retrospective cohort study from the CCSS, Green et al. showed that the risk of obesity was decreased among those who met the US Centers for Disease Control and Prevention guidelines for vigorous physical activity (RR=0.90 ; 95%CI : 0.82-0.97).[17] See Table 1.

Promoting health protective behaviours

In a behavioural health promotion study by Hudson et al., on 266 childhood cancer survivors, aged 12 to 18 years from the St. Jude Children's Research Hospital, authors assessed the impact of an intervention which was a multi-component behavioural intervention on changing health knowledge, health perceptions (perceived susceptibility, perceived seriousness, perceived benefits, perceived barriers), and health behaviour practices. In this study, more than half of the participants (52%) didn't know that cancer treatments could be associated with a risk of 2nd cancer; 48% of the participants considered this risk as the most concerning potential treatment sequelae (see Table 1).[35] Due to lack of knowledge about the long term side effects of treatments and about the risk associated with some behaviours, AYAs may not adopt healthy behaviours. New internet technologies ('ehealth') seem to be useful to promote healthy behaviours in children and AYAs who have had cancer.[36]

Discussion

The aim of this article was to review the available literature on cancer risk factors (lifestyle and occupational exposures) in children and AYAs previously treated for cancer. Our article also reviews the interventions that can be implemented to improve healthy behaviours in this population.

It seems that the behaviour of cancer survivors towards a healthy lifestyle is similar to that of the healthy population of the same age in particular regarding tobacco smoking, diet, and may be to a lesser extent with sun exposure. Although AYA cancer survivors seem to have lower physical activity than their peers, these results are consistent with previous literature that reported a significantly higher prevalence of current smoking, obesity and chronic conditions in this population compared with individuals who have no history of cancer.[37]

Overall, there are few studies that investigate the risk factors associated with 2nd malignancies, except for long term side effects of cancer treatments, which are the most important risk factors. However, the increased incidence of second malignancies in this population, of all cancers and in particular of cancers not associated with primary treatment, suggest a potential role of and synergies with other cancer risk factors, such as lifestyle and occupational exposures. The role of the latter in the development of second malignancies remains widely unknown.

Smoking in children and AYA cancer survivors may increase the risk of lung cancer, breast cancer, colorectal cancer and leukemia.[6] Smoking is one of the most preventable risk factor implicated in cancer development. While survivors of childhood cancer have similar smoking rates to their peers, the former seem to have a better knowledge of the health risks associated with smoking. Tobacco has not only a carcinogenic effect per se, but also enhances radiation effects. For example, smoking has been shown to increase the risk of radiotherapy induced lung cancer in patients treated for Hodgkin's disease.[36] While few studies have assessed the usefulness of smoking cessation programs in young cancer survivors, short term results are quite disappointing and there is no long term evaluation.[28,30] The use of NRTs in this population seems premature.[32] This means that it is important to improve our knowledge on the role of tobacco in the occurrence of 2nd malignancies and to implement specific interventions to reduce tobacco consumption and to prevent young people from starting smoking.[10] This may equally apply to the use of cannabis.

Alcohol consumption appears to contribute substantially to the worldwide cancer burden although light to moderate alcohol consumption has been associated with some benefits related to heart disease, stroke and diabetes (benefits that are reversed with occasional or regular heavy drinking), as highlighted by Cogliano et al.[38] Alcohol consumption is associated with an increased risk of 2nd malignancy in adults treated for cancers of the upper aerodigestive tract.[39] Even if alcohol consumption seems lower in childhood or adolescence survivors cancer compared to the healthy age-matched population,[11,12] it may contribute to increase risk of 2nd malignancies. However, no study has specifically evaluated the impact of alcohol consumption on the risk of 2nd malignancy in that population.

The lack of physical activity has been shown to be associated with an increased risk of 2nd malignancies in breast cancer patients.[40] Also, obesity and lack of physical activity are known risk factors for cancers frequently found in childhood or adolescent cancer survivors, such as breast cancer, colorectal cancer and lung cancer.[39] Furthermore, weight gain associated with cancer related treatments (steroids or brain radiotherapy) can be amplified by an unhealthy diet and lack of physical activity.[25] However, we found no studies investigating specifically their impact on second malignancies in childhood and AYA cancer survivors. Yet, prevention programs focusing on diet and physical activity have shown long-term efficacy in young people without cancer.[40] It would be pertinent to study the impact of treatment related weight gain and its active management on second malignancies.

The literature suggests greater proportions of childhood and AYA cancer survivors with appropriate behaviour towards UV exposure in young cancer survivors. However, there is still progress to be

made regarding the use of artificial tanning devices. Information on the risk of skin cancer associated with inappropriate sun exposure and artificial UV exposure should be given to these patients.[23,41] Also, such information should explain the importance of balancing natural sunlight exposure to avoid its damaging effects and meet sun protection guidelines with vitamin D requirements. The latter produced by natural sun exposure may have a protective effect against certain types of cancer.[42]

Although AYAs are about to enter the workforce in most cases, there are no studies about the impact of occupational exposures on the risk of relapse of the first primary and on the risk of second malignancies. However, some of the tumours that occur in childhood cancer survivors (such as lung tumours) can be related to carcinogens that can be found in the occupational environment. According to the periodical cross-sectional French medical survey on exposure to occupational risks (SUMER), young apprentices and young workers are the most exposed to carcinogens at work.[43] Therefore as a precautionary measure, they should be advised to talk about their medical history with an occupational physician when thinking about their professional orientation. There are no jobs contraindicated in cancers survivors, however applying a precautionary principle, specific attention should be paid in this population to avoid occupational exposure to carcinogens.

While the awareness of cancer risk among survivors of childhood and adolescence cancer is higher than in the general population, a large proportion of the former seems not aware of their increased risk of 2nd malignancies.[35] Various studies emphasize the need to implement specific prevention programmes for this population to increase the awareness, in particular the risks associated with certain lifestyle factors and to try and reduce them.[32]

While there is no data on the timing of preventive information and interventions, patients request such information from their clinical team.[15,41] International and national guidelines on prevention for this population, including screening guidelines, have been (http://survivorshipguidelines.org) (http://www.sfce.org). It is important that this information be communicated and discussed several times throughout follow-up. General practitioners (GP) have also a key role in providing these guidelines as less than 20% of adults who had a tumour in their childhood are followed in a specialized centre or by an oncologist.[45] This percentage even decreases over time. Thus GPs are in front line to implement prevention and screening procedures and detect 2nd malignancies for which late diagnosis is a poor prognostic factor.[45] However, GPs often do not feel comfortable following up childhood and AYAs cancer survivors as they lack information on long term side effects and appropriate follow-up schedules.[45]

A recent workshop of the Institute of Medicine emphasized the importance to improve AYAs cancer survivorship care based on '*a systematic plan for screening, surveillance, and prevention that*

incorporates risks based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviours, and comorbid health conditions should be developed for all AYA cancer survivors'.[46]

It may be timely to develop and implement specific prevention approaches in this population, such as lifestyle intervention programs and to evaluate their benefits, especially since many lifestyles risk behaviours cluster together.[47] The development of evidence-based programs such as developed and tested by Emmons et al. to address substance abuse among AYA cancer survivors,[46] should be encouraged to be widely implemented in other countries.

It seems relevant to study how to improve adherence of children, adolescents and young cancer survivors to these prevention guidelines. Adolescents seem more receptive to messages given by people of their age. Newer information and communication techniques (such as social networks, games, text-messages or smartphone applications) could be used to deliver the information and some of the interpersonal interactions required. As noted by Elliot et al., health promotion strategies in childhood ALL survivors relate to strategies similar to those applicable to improving healthy behaviours in the general population; and strategies using eHealth technologies are promising.[36] In a recent survey in 25 European states, on over 25000 children aged 9 to 16, 93% surfed on internet at least once a week and 60% every day or nearly. They spend at least 1 hour and a half per day on internet. Half of them say "they feel more themselves" in relationships on the net than face to face. Adolescents qualify the net as being the 1st source of information concerning health.[48] Therefore this technology, with games or online quizzes, may be a good mean to convey messages on prevention and healthy lifestyles (cannabis, drug abuse, sexuality, diet, physical activity…).[49,50] These tools may be also useful for social support and sharing experiences to reinforce motivation. They are also a great opportunity for new interdisciplinary public health approaches to prevention.

Conclusions and perspectives

The risk of second malignancies after a childhood or AYAs cancer is an important issue in this population and should be addressed in follow-up programs. Appropriate communication between oncologists and GPs is very important in this context. Patients (and their GPs) should have all the information on the course of the disease, the treatment received, the possible late side effects, the follow-up plan and the screening plan. This plan should be adapted to the individual's risks and the evolution of risky exposures and behaviours.

Our review underscores the need to improve our knowledge on the impact of these behaviours (tobacco, alcohol, diet and physical activity) on second malignancies and their interaction with the effects related to treatment.

It is important to implement specific prevention strategies in this population, evaluate these interventions and the factors that could contribute to adhesion to health-promoting messages relying in particular on research on health-risk behaviours that are commonly initiated during pre-adolescence and adolescence and that have importance for adult risk of second primary cancers.

The conclusions of our review may evolve as new data will become available.

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