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Review

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## Abstract

**Background**: Adolescents and young adults with cancer have special characteristics and needs.

**Aims**: This study highlighted psychosocial challenges, fertility issues and secondary diseases encountered in adolescents and young adults with cancer. This work is meant to be a platform for future interventions for cancer in this demographic.

**Methods**: We investigated the latest edition of the Jordan Cancer Registry (JCR) and our more comprehensive institutional database during 2000–2012. Smoking, obesity and fertility preservation were addressed briefly as important issues among AYA patients.

**Results**: Cancer among adolescents and young adults represents 16.3% of all new cancer cases and has increased by 25% over the past 12 years. Women are more likely to be involved (female: male ratio of 1.44: 1) because of thyroid and breast cancers. Five-year survival rate for the AYA group was 72.4%, which was significantly better than for adults aged ≥ 40 years (59.8%) but worse than for paediatric patients aged

**Conclusions**: Cancer in adolescents and young adults represents a substantial and growing

proportion of oncological diagnoses. Due to their special needs and treatment complications, a dedicated service is urgently needed.

Keywords: Cancer; Jordan; adolescents, survival, registry

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## Introduction

Cancer is one of the leading causes of morbidity and mortality in Jordan. Latest national mortality data showed that cancer accounts for 16.5% of all deaths, next only to cardiovascular disease, which claims more than one third (38.4%) of the total national mortality (1).

Adult oncologists usually deal with older patients who tend to have the highest incidence of cancer, and paediatric oncologists tend to focus on younger age groups. Thus, many of the issues related to older paediatric patients and younger adults are lost in between. Ferrari et al. described this situation as: “Adolescent patients with cancer reside in a ‘no-man’s land’ between the world of paediatric oncology and that of ‘adult’ medical oncology” (2). Additionally, adolescent and young adult (AYA) patients are underrepresented in clinical trials and that might explain the lack of progress in treatment outcomes in this age group (2,3). The field of AYA oncology is evolving rapidly and has become a focused subspecialty.

In Jordan and many neighbouring countries, the definition of paediatric patients is inconsistent.

We use 18 years of age as the cutoff at our centre, however, many hospitals and healthcare facilities, including the Ministry of Health and military and university-based hospitals in the country treat patients above the age of 13 years as adults. There is significant variation in the definition used to describe the age of the AYA cancer population. The National Comprehensive Cancer Network (NCCN) (4) and National Cancer Institute (NCI) (5) define AYAs as 15–39 years, and as such, reported that ~70 000 young patients are diagnosed with cancer each year in the United States of America (USA), which accounts for ~5% of all cancers diagnosed. Other researches and health organizations, including the World Health Organization (WHO) (6) and the Surveillance, Epidemiology and End Results (SEER) programme (7), use different definitions of 15–25 and 15–29 years, respectively.

Tumour biology and treatment outcomes vary among different age groups. Thus, an age-specific approach is needed when dealing with these cancers; acute leukaemia is a good example (8–10).

Fortunately, treatment outcomes in childhood and adolescent cancer tend to be significantly better compared to those in older adults. Many younger patients survive, which highlights the need for a structured survivorship programme that takes into account the many specific issues related to their cancer and its treatment-related late complications; both physical and psychosocial (11,12). This retrospective study and literature review aimed to address such specific issues. It is hoped that this work may stimulate more research in this important field, especially given that most of our population is within this younger age group.

## Methods

We utilized the latest edition of the Jordan Cancer Registry (JCR) report published in 2012 (13). The JCR report stems from an annual population-based registry that was established in 1996 under the jurisdiction of the Ministry of Health. We identified all cancers reported by the JCR in the 15–39-year age group for the period 2000–2012. The national registry does not report treatment outcomes or survival data, so these data were collected using our own institutional cancer registry that was started in 2006. This represents > 60% of the total national cancer patients and is matched to the dataset used to generate the JCR report. The cases registered within our cancer centre had their diagnosis confirmed and all their treatment and follow-up in our institution.

Pubmed/Medline was searched for all published literature using the key words: Cancer; Jordan; Adolescents, Survival and Registry. Abstracts presented at major international conferences were also reviewed.

Descriptive statistics were performed for all variables. Results for continuous variables were expressed as median (interquartile range). Categorical variables were expressed as numbers (percentages). The Kaplan–Meier method was adopted to estimate overall survival (OS) curves, and a log-rank test was used to compare patients' survival times between age groups. OS was calculated from the time of primary diagnosis to death from any cause or to the last contact based on the patients' status (dead or alive). A significance level of $P \leq 0.05$ was used in the analysis. All curves were created using GraphPad Prism version 6 (La Jolla, CA, USA), and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Results

A total of 5013 new cancer cases were recorded in Jordan in 2012. Median age at diagnosis was 56 years, with considerable variation according to the cancer site and sex (60 years for men and 53 years for women) (13). In 2012, the crude incidence rate of all cancers among Jordanians was 78.5 per 100 000 (71.2 for men and 86.2 for women). The age-standardized rate (ASR) adjusted to the World Standard Population was 133.4 per 100 000 population (126.1 for men and 141.4 for women) (13).

There were 815 AYAs, aged 15–39 years, diagnosed with cancer throughout Jordan in 2012. This represents 16.3% of the total number of cancer cases diagnosed during this period ( Table 1 ). The female: male ratio was 1.44: 1. This female predominance was evident across all age subgroups and was mostly due to the high percentage of breast and thyroid cancers in women in the AYA age group.

Breast cancer, thyroid cancer and Hodgkin's lymphoma were the most common cancers in women in the AYA group, while testicular cancer, leukaemia and lymphoma were the most commonly encountered tumours among men ( Figure 1 ).

Since the introduction of the population-based national cancer registry in 1996, the total number of reported cases of cancer has increased from 3362 in 2000 to 5013 in 2012; a 49% increase. A similar increase was also noted in the AYA group, albeit at a slower rate. Cancer cases have increased from 654 in 2000 to 815 in 2012; a 25% increase. Much of this increase was in the older age groups of 30–34 and 35–39 years ( Figure 2 ). The number of cases did not increase as much in the younger age groups (15–29 years).

Survival data were available for 10 328 patients; 2194 (21.2%) of them among the AYA group ( Figure 3A ). All were diagnosed, treated and followed up at our institution. Five-year OS for the AYA group was 72.37%, which was significantly better than for adults aged ≥ 40 years (59.75%) but worse than for paediatric patients aged Figure 3B ).

## Discussion

Survival of AYA patients with cancer is significantly better than in older age groups. Even among the AYA age group itself, patients aged ≤ 30 years have better survival than those aged > 30 years. Such findings can be explained by the types of cancer encountered and absence of comorbidity in this age group. A total of 4.1 million (43%) Jordanians are within the AYA age group, which means that Jordan, like many other countries in the Eastern Mediterranean Region, can be considered to have a young population. Although the incidence of cancer in this age group is lower than in older people, many special issues are encountered in routine clinical practice that are worth highlighting.

Women are more affected than men because of breast and thyroid cancer. This highlights the importance of issues like fertility preservation among young women, and many are exposed to therapies that can negatively affect their fertility. In the following paragraphs we address issues related to breast cancer as the commonest cancer in this age group, followed by a brief discussion of late effects of childhood cancers, smoking, obesity and fertility preservation.

### Breast cancer

Breast cancer remains the most common cancer among women, even in the AYA group. In Jordan and many neighbouring countries, breast cancer tends to be diagnosed at an earlier age. As reported by the JCR, the median age at diagnosis had not changed over the last 12 years and remains at 50–51 years (13). In 2012, 149 breast cancer cases were reported among AYAs, representing 18.3% of all cancers in this age group and 14.8% of all breast cancer cases. In western societies, only 7.0% of all female breast cancer is diagnosed in women aged

Breast cancer in younger patients tends to be associated with more aggressive features (15–17), leading to poorer prognosis and a need for more aggressive treatment, which results in a higher likelihood of long-term treatment-related toxicity, and unique psychosocial concerns (18).

Additionally, familial breast cancer is more common in this age group. Over 10–15% of breast cancer patients carry high-risk mutation genes like BRCA-1 and BRCA-2 (19). Given the high penetrance rates among such mutation carriers (20,21), it is important to identify patients for whom many additional risk-reduction interventions, like bilateral mastectomy and oophorectomy can be considered.

Breast reconstruction following surgery in the diseased breast or prophylactic mastectomy is important, especially in young patients. Such surgery cannot be performed without the appropriate setup that includes a multidisciplinary team approach with full psychosocial support that should also address financial cost. Most reconstructive procedures and prophylactic surgery are usually denied by almost all local private and governmental health insurance plans.

### Late effects of childhood cancer

Late effects of childhood cancer treatment are well recognized and defined as adverse effects with onset ≥ 5 years after completion of therapy. However, this problem is not sufficiently addressed in cancer care in developing countries. The Childhood Cancer Survivor Study initiated in 1994 is the main source for understanding these late effects (22). Large cohorts of survivors were collected and followed longitudinally. In its initial phase, the study included > 14 000 survivors who were treated between 1970 and 1986. More recently, the study has expanded to include 10 000 more survivors diagnosed between 1987 and 1999 (23). Premature menopause, stroke, and second cancers were among the common potential late effects. Childhood cancer survivors should receive close, long-term follow-up, which is not routinely available.

### Smoking

The association between tobacco smoking and cancer is well established. In a study reported in 2012, approximately half (45%) of the Jordanian population had smoked a cigarette in the past month, 40% in the past week, and 36% in past 24 hours (24). Waterpipe tobacco smoking is becoming popular in Jordan and neighbouring countries, especially among AYAs. In another study reported in 2014, 1845 students from 4 local universities were randomly recruited. Waterpipe tobacco smoking rates were 30% in the past 30 days and 56% ever, while cigarette smoking rates were 29% in the past 30 days and 57% ever. Past 30-day waterpipe tobacco smoking rates were 59% for men and 13% for women (25). In a third study conducted among 547 students in local dental schools, 54.3% of men and 11.1% of women reported current tobacco use. The majority had used both cigarettes and waterpipe tobacco. Nearly half of the women reported that they smoked at home in the presence of their parents (26). These findings underscore the extent of the smoking problem in our population, especially among the younger age groups, and the urgent need for effective smoking cessation interventions.

A national cancer control programme does not exist in Jordan. However, a tobacco control programme was recently established to help increase public awareness of the hazards of smoking and to introduce new legislation that prohibits smoking in public places. However, compliance with such programmes is still poor.

Although no official data exist on the smoking rates among AYA cancer survivors, it is expected to be high. The physical and psychosocial complications that result from cancer treatment places stress on patients, especially younger ones, that may encourage them to smoke, especially within a society that views smoking as a common cultural habit. This is an important issue to recognize as the late complications of AYA cancer treatment, such as coronary artery disease and stroke, are likely be higher with smoking.

**Obesity**

Obesity continues to represent a significant public health problem and has recently grown into a major global health epidemic (27). In the USA, more than two thirds of adults are now overweight and one third is obese. It is also estimated that one third of children and adolescents in the USA are either obese or overweight (28). In a more recent report, the prevalence of obesity among children and adolescents aged 2–19 years was 17.0% and extreme obesity was 5.8% (29). Obesity in Jordan and many neighbouring countries is also common. In a study that included 2836 subjects aged ≥ 25 years conducted in 4 Jordanian towns, the overall prevalence of obesity, defined as body mass index ≥ 30 kg/m2, was 49.7%. Obesity was more common in women (59.8 vs 32.7% in men) (30). More recent studies have reached similar conclusions (31,32).

Cancer treatment, directly or indirectly, can lead to overweight and obesity. Steroids are active components of many chemotherapeutic regimens and are widely prescribed as antiemetic therapy. Cranial irradiation for childhood cancer appears to have the greatest influence on obesity in adult life. In a study reported in 2015, 47% of those who received this form of treatment became obese compared with 29.4% who did not (33). A retrospective study in 2003 compared 1765 adult survivors of childhood acute lymphoblastic leukaemia, whose treatment protocol included cranial irradiation, to 2565 adult siblings of childhood cancer survivors (34). The odds ratio for being obese in survivors in comparison with siblings was 2.59 for women and 1.86 for men. The risk of obesity was greatest among women diagnosed at 0–4 years of age and treated with radiation doses ≥ 20 Gy.

Even in children and adolescents, obesity is associated with many comorbidities including gastrointestinal, endocrine, cardiovascular, orthopaedic, pulmonary, neurological, dermatological and psychosocial problems (35). In addition to these serious medical problems,

direct medical cost and economic impact related to obesity and its associated problems put a lot of pressure on healthcare budgets (36).

Many large epidemiological studies have clearly shown that obesity is a major modifiable risk factor for many cancers including, but not limited to, cancer of the endometrium, colorectum, kidney, oesophagus, breast and pancreas (37–40). Moreover, obesity can be a poor prognostic factor and contributes to the unfavourable survival rates in obese patients with cancer (38,41–43). Higher likelihood of comorbidity and unfavourable tumour characteristics and a tendency to underdose chemotherapy in obese patients may contribute to such poorer survival rates, particularly among breast cancer patients (44,45). With the earlier onset of overweight and obesity, often occurring during childhood, there is a concern that the effects of obesity on cancer outcomes are even worse. Although we do not have strong evidence that weight loss is associated with better cancer survival, improved diet and greater physical activity associated with weight loss do have clear health advantages.

Given the above problems, there is an urgent need to implement health programmes to prevent and control overweight and obesity at a national level (46). Counselling with a dietician and establishment of an exercise programme should be routine components of the multidisciplinary approach to cancer. Oncologists should devote enough time to discuss weight loss with their overweight patients with cancer (47).

**Fertility preservation**

Over recent decades, survival rates for most cancers have significantly improved and more younger patients survive their disease. Many of the cancer treatment methods, especially chemotherapy, can have a negative impact on fertility both in men and women. There are established means of preserving fertility prior to cancer therapy. Sperm cryopreservation is routinely practiced in young men and in vitro fertilization and embryo cryopreservation are widely available for young women. Several innovative techniques, including ovarian tissue cryopreservation, are being actively investigated. Current techniques are limited by the patient's sexual immaturity, and all available approaches for children are experimental (48,49). Several studies have shown that gonadotropin-releasing hormone agonists when used with chemotherapy protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility (50).

Several factors may contribute to low compliance rates. Impaired future fertility is difficult for children to understand although outcomes are potentially traumatic to them as adults (51). Additionally, patients may not be aware of the potential fertility loss and such problems may not be communicated well by the treating physicians (51, 52). Patients and families are usually

overwhelmed and focus exclusively on the cancer diagnosis and treatment and may be concerned that pursuing fertility preservation will delay their treatment, thus negatively affecting their cure rates (53–55). In a web-based survey from the Dana–Farber Cancer Institute, Boston, USA, in 2010, only 29% of 657 breast cancer patients with a mean age at diagnosis of 32.9 years reported that infertility concerns influenced their treatment decisions (56). In 2013, the American Society of Clinical Oncology (ASCO) issued updated guidelines recommending that providers discuss fertility preservation with all patients of reproductive age who will be receiving cancer treatment with a possible risk of iatrogenic infertility. However, compliance with such recommendations is still poor, even in western societies (57). In another study, 201 patients aged 13–50 years who received a new cancer diagnosis and planned to initiate curative chemotherapy at the University of North Carolina were reviewed (58). Only 59 (29%) received fertility counselling and 23 (11%) attempted sperm banking. Younger patients were significantly more likely to be counselled, with mean ages of 27.4 and 40.4 years for counselled and noncounselled patients, respectively. Among counselled patients, those with a lower median income or who had Medicaid or no insurance were less likely to bank sperm.

The present study and many others (59–61) clearly demonstrate the low referral rates for fertility counselling and fertility preservation. Improved education for providers, system-wide interventions, implementing standardized processes for sperm and ova preservation, and the institution of fertility preservation programmes will hopefully increase referral for such services.

## Conclusion

More than 40% of the Jordanian population are within the AYA age group. Fortunately, the cancer incidence in this age group is lower and their survival is better than in older adults. Smoking, obesity and fertility preservation are among many other important issues in this age group. Specialized ancillary services addressing these issues need to be incorporated into multidisciplinary teams treating such patients, leading to the establishment of comprehensive AYA cancer programmes.

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**Competing interests**: None declared.

Soins du cancer chez l’adolescent et le jeune adulte en Jordanie

## Résumé

**Contexte** : Les caractéristiques et les besoins particuliers des adolescents et des jeunes adultes atteints de cancer sont spécifiques.

**Objectif** : La présente étude a mis en évidence les difficultés psychosociales, les questions liées à fécondité et les pathologies secondaires auxquelles font face les adolescents et les jeunes adultes atteints de cancer. Ce travail a été conçu pour servir de tremplin à de futures interventions en faveur d'un traitement anticancéreux destiné à cette tranche de population.

**Méthodes** : De 2000 à 2012, nous avons basé notre étude sur la dernière édition du Registre national du cancer de Jordanie, ainsi que sur notre base de données institutionnelle, plus complète. Les questions liées au tabagisme, à l'obésité et à la préservation de la fécondité chez les patients appartenant au groupe des adolescents et des jeunes adultes ont été brièvement traitées et considérées comme des problèmes importants.

**Résultats** : Le cancer des adolescents et des jeunes adultes représente 16,3 % de tous les nouveaux cas de cancer et cette proportion a augmenté de 25 % ces 12 dernières années. Le risque d'atteinte est plus élevé chez les femmes (le ratio femmes-hommes étant de 1,44 : 1) en raison des cancers de la thyroïde et du sein. Le taux de survie à cinq ans pour le groupe des adolescents et des jeunes adultes était de 72,4 %, taux significativement plus élevé que celui présenté par les adultes de 40 ans et plus (59,8 %), mais moins favorable que celui des patients pédiatriques de moins de 15 ans (79,2 %) (p

**Conclusion** : Le cancer des adolescents et des jeunes adultes représente une part notable et croissante des diagnostics oncologiques. Étant donné qu'il implique des besoins et des complications de traitement particuliers, il est urgent de créer un service consacré à cette tranche de population.


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WHO EMRO | Cancer care for adolescents and young adults in Jordan

: أبرزت هذه الدراسة التحديات النفسية والاجتماعية وقضايا الخصوبة والأمراضالهدف
الثانوية التي يواجهها المراهقون والشباب المصابون بالسرطان . وتهدف هذه الدراسة
لإرساء منصة تنطلق منها التدخلات المستقبلية للسرطان في هذه المجموعة السكانية .

: درسنا أحدث إصدار من السجل الأردني للسرطان وقاعدة البيانات المؤسسيةطرق البحث
الأكثر شمولية لدينا خلال الفترة 2000-2012. ودرسنا بإيجاز قضايا التدخين والسمنة
والمحافظة على الخصوبة باعتبارها قضايا مهمة بين مرضى السرطان المراهقين والشباب .

: يمثل السرطان الذي يصيب المراهقين والشباب ٪ 16.3 من مجموع حالات السرطانالنتائ ج
الجديدة، وقد زاد بنسبة ٪ 25 خلال السنوات الاثنتي عشرة الماضية . واتضح من الدراسة أن
إصابة الإناث أكثر احتمالاً من إصابة الذكور ( نسبة الإناث إلى الذكور 1.44 إلى 1) ، وذلك
بسبب سرطان الغدة الدرقية وسرطان الثدي . وكان معدل البقاء على قيد الحياة لمدة 5 سنوات
لدى مجموعة المراهقين والشباب ٪ 72.4 ، وهو أفضل بمقدار يعتدّ به مما لدى البالغين في
عمر 40 عاماً أو أكثر (59.8 ٪) ، ولكنه أسوأ لدى الأطفال الذين تقل أعمارهم عن 15 عاماً
(79.2٪ ) وكان (P

الاستنتاج : يمثل السرطان في المراهقين والشباب نسبة كبيرة ومتنامية من تشخيصات
الأورام . وتمسّ الحاجة إلى إنشاء وحدة مخصصة لهم بسبب احتياجاتهم الخاصة ومضاعفات
العلاج لديهم .

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