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Colorectal Secondary Malignancy Risk Estimates Following Radiation Therapy: A Prospective Cohort Study Among Cancer Survivors In Saudi Arabia*

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Abstract: Radiation-induced second cancer is one of the crucial late side effects of radiotherapy treatment of first cancer. Although the mechanism behind the induction of secondary cancers is not yet well understood, several factors are associated with their occurrence, such as age at exposure, radiation dose to the organ and surrounding tissues, treatment modalities, and family history of cancer. This study aims to provide long-term estimates of second cancer incidence amongst colon cancer survivors in Saudi Arabia. The lifetime attributable risk (LAR) after radiation treatment of colon cancer was determined, between the age at exposure and up to 95 years, in a single-institution cohort of male and female cancer survivors whose age at treatment was in the range of 43 to 85 years. The risk estimates varied significantly based on age at exposure, gender, and organ dose.

Keywords: Colorectal cancer; Radiotherapy; Dose; Second cancer incidence; Lifetime attributable risk

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1. Introduction

Colon cancer and rectal cancer, collectively known as colorectal cancer (CRC), are the third and second most frequently occurring cancers worldwide in men and women, respectively, and the second deadliest malignancy overall [1]. In 2020 over 1.9 million new CRC cases were diagnosed worldwide. With over 0.9 million deaths, CRC remained the second cause of cancer death after lung cancer for both sexes [2]. The highest incidence rates have been found in Australia, New Zealand, Canada, and the United States, and the lowest in China, India, Africa, and South America. Genetic and environmental factors both play an essential role in the etiology of CRC [3]. Most CRCs are erratic and strongly linked to environmental factors where obesity, smoking, consumption of processed meat, and alcoholic drinks are the main factor risks. There are striking differences in CRC incidence among different races and ethnic groups. Clinical indications showed they are relatively unusual before the age of 50 and commonly evolve, in the 10 to 15-year period, from adenomatous polyps to invasive carcinoma [4, 5]. A small percentage of CRC cases are attributed to inherited syndromes and familial clustering without a recognizable inherited syndrome [6]. Survival rates have drastically increased over the past three decades, especially in developed countries, owing to continuous progress in the prevention, early-stage diagnosis, and treatment [7].

1.1. CRC types

The transformation of the normal colonic epithelium to a precancerous lesion (adenoma) and ultimately to invasive carcinoma requires an accumulation of genetic mutations, either somatic and/or germline [8]. The occurrence of CRC can be categorized in three main molecular pathways based on the somatic and genetic disruptions in DNA repair pathways [9, 10].

- Chromosomal instability (CIN) is described by an aneuploidy sub-chromosomal genomic amplifications and a high frequency of loss of heterozygosity in tumor suppressor genes or protooncogenes such as *TP53* or *KRAS*, respectively. This more aggressive multistep carcinogenesis cancer is the most common, around 70%, of all the sporadic CRC [11].
- Microsatellite instability (MSI) pathway due to loss of DNA repair mechanisms affecting coding microsatellites in mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*. There is a growing body of evidence showing that hypermethylation of CpG islands in these genes inhibits their expressions [12]. This heritable germline mutation, found in Lynch syndrome, a hereditary non-polyposis colorectal cancer (HNPCC), is responsible for 20% of CRC.
- Epigenetic instability CpG island methylator phenotype (CIMP) pathway caused by the hypermethylation of protooncogenes and tumor suppressor genes leading to the inhibition of their genetic expressions. This gene silencing pathway is responsible for 10% of all CRC [13].

1.2. Biological pathways of CRC induction

Radiation-induced cancer is a slow and multistep process. There is a growing body of evidence showing that the risk of developing

a second cancer in the irradiated tissue or the adjacent organs is conceivable and increases over time [14]. Radiation exposure of the highly radiosensitive gastrointestinal track tissues to ionizing radiation induces, via inherent DNA damages and variety of cellular responses, a premature cell senescence promoting the transition from normal epithelium cells to malignant tumor cells in the colorectal site [15]. The oversecretion of cytokines (IL-1, IL-6, IL-7, IL-13), chemokines (CCL2, CXCL1, CXCL8, CXCL12), and growth factors (heregulin, EGF, bFGF, IGF, VEGF, TGF-β1) by senescent cells activates the NFκB nuclear transcription factor pathway, suppressing cancer cell apoptosis and contributing to the majority of CRC recurrences [16].

Furthermore, activation of NF-κB induces, via cytidine deaminase (AID), mutations in the tumor suppressor gene *TP53* [17] making senescent cells escape growth inhibition checkpoints leading to accelerated colorectal tumorigenesis where *TP*53 mutations is present in 40% of CRC [18].

1.3. CRC incidence and mortality in Saudi Arabia

In Saudi Arabia, the most common cancer diseases include breast, thyroid, and CRC. The latter is the highest and the third common cancer amongst men and women, respectively. The age-standardized incidence rates and age-standardization mortality rates for CRC are 13.1 and 6.3 cases per 100,000 people for both sexes [6]. Risk factors such as excess weight, sedentary lifestyle, diet rich in processed food, smoking, inflammatory bowel disease were found to contribute to 60–65% of CRC for all genders [19]. Family history, likely influenced by the high rate of consanguineous marriages, along with genetic syndromes (such as familial adenomatous polyposis or Lynch syndrome), account for 25–30% and 5% of cases, respectively [6, 19, 20]. Polymorphisms of the protein encoding genes ADIPOQ, XRCC1 and RETN, and vitamin D receptor VDR due to low vitamin D intake, have also been associated with increased risk CRC among Saudi older population [21, 22].

To reduce the national incidence of CRC, a large screening program targeting both men and women aged 40 and above was launched a decade ago [23, 24]. However, public perception and lack of acceptance of screening colonoscopy for CRC remains the main obstacle for the success of this program.

Saudi patients diagnosed with an advanced stage of CRC are at younger ages (less than 50 years) when compared to western populations [25]. Mansoor et al. [26] and Aljebreen [27] reported that 39 and 37% of their patients were under 50 years old, respectively. Al-Ahwal and Al-Ghamdi [28] reported that 29.7% of CRC Saudi patients were younger than 40 years old. Population-based cancer incidence showed that CRC suffered the sharpest increase from age 40 years to 50 for all genders (4-fold and 3-fold for male and females respectively), becoming a major healthcare burden [29].

2. Methodology

2.1.Data collection

The retrospective cohort study included a large number of males and female patients, ranged in age from 43 to 85 years, and from 43 to 73 years of age, respectively all taken

from King Abdullah Medical City – Oncology center (Jeddah, Saudi Arabia) Cancer Registry 2016-2018, with a confirmed first CRC. The patients underwent Linacbased intensity-modulated radiation therapy (IMRT) with an average fractionated dose of 1.8 Gy, and total treatment doses ranging from 30 to 70 Gy. The dose delivery was generally well tolerated by the patients. Radiation exposure was ascertained by the effective dose (ranging from 3.6 to 8.4 Sv), which quantifies the biologic effects of radiation absorbed by the anatomic region irradiated. The dose selection was tailored to patient-specific parameters, including the nature of the underlying condition, age, tumor size, and tumor location.

2.2.Modeling of risk estimations

CRC has been noticeably correlated with radiation exposure in Hiroshima and Nagasaki A-bomb survivors' data during the period 1950 – 2000 [30]. Furthermore, several large epidemiologic studies and predictive models have shown that long-term survivors of colon radiotherapy have an increased incidence of second cancer, mainly located within or close to the primary cancer treatment field [31, 32, 33]. Based on this, a number of risk models have been developed by international bodies: the International Committee on Radiation Protection in its publication 103 [34], the United Nations Scientific Committee on the Effects of Atomic Radiation in its Report 2006 [35] and the Biological Effect of Ionizing Radiation in its report BEIR VII [36] to estimate second CRC incidence risks. The uncertainties associated with each of the models were close to or exceed the variation between the models [37].

2.3.Application of the BEIR risk model to CRC incidence

Although initially developed for low-dose radiation exposures, we used the BEIR VII linear no-threshold (LNT) model to estimate the probabilistic risk of a second CRC associated with radiotherapy doses, as it provides parameters for specific organs for each sex as well as parameters describing incidence with age at exposure and attained age. The BEIR VII cancer risk is expressed using both multiplicative and additive models [38]. In the multiplicative model, the incremental site-specific cancer risk is proportional to baseline rates. In the additive model, the risk increment is independent of the baseline rates but adds to it. To the best of our knowledge, this is the very first study to address the occurrence of second CRC amongst Saudi cancer survivors following external radiotherapy.

For all solid carcinogens, it is agreed that the risk increases with dose, with a latency period of 5 years [38]. Both excess absolute risk (EAR) and excess relative risk (ERR) (see glossary) of secondary solid cancer were calculated according to

$$EAR \text{ and } ERR = \beta_s (OED) e^{\gamma e^*} \left(\frac{a}{60}\right)^{\eta}$$

$$e^* = \frac{(e-30)}{10}$$

for $e < 30$ and 0 for e > 30 years

where e is the age at exposure (years), $a = e + L$ is the attained age (years), L the minimum latency period at which a solid cancer might occur following radiotherapy treatment (5 years for solid cancers). β_s, γ and η are the BEIR VII specific cancer risk

coefficients associated with sex, age at exposure and attained age, respectively. There is no increase in risk in the absence of exposure *i.e.* both ERR and EAR = 0.

The LAR describes the probability that an irradiated person would develop a second cancer during his/her lifetime (total projected second cancer risk). It is calculated over the age range of $(e + L)$ to 95 years using the values of EAR and ERR

$$LAR = \left(\sum_{a}^{95} ERR.\lambda_a^s.\frac{S(a)}{S(e)}\right)^{0.7} \times \left(\sum_{a}^{95} EAR.\frac{S(a)}{S(e)}\right)^{0.3}$$

λ_a^s is the baseline cancer rate, *i.e.* the cancer rate incidence in the absence of irradiation, which depends on sex (s) and attained age (a), $S(a)$ is the probability of surviving until age a, and $\frac{S(a)}{S(e)}$ is the probability of survival a healthy individual to age a conditional on survival to exposed age e. Values of λ_a^s were taken from the Saudi National Health Information Center - Cancer Registry [39]. An average value of 44.6% for both males and females was taken for the value of $\frac{S(a)}{S(e)}$ [25, 27]. Projections of the lifetime risk of CRC, are weighted in the logarithmic space by 0.7 and 0.3, for the additive and multiplicative models, respectively. The coefficients used for estimating ERR and EAR of developing a second CRC are given in Table 1. Data entry and processing were performed using Excel 2010 by Microsoft.

The age-specific baseline cancer rate or baseline prevalence, by five-year age groups for both male and female Saudi population diagnosed with CRC is shown in Table 2 [39].

Table 1. Coefficients of the BEIR VII cancer risk model for CRC

Model	ω	β_M	β_F	γ	η
ERR	0.7	0.63	0.43	-0.30	-1.4
EAR	0.3	3.2	1.6	-0.41	2.8

Table 2. Age-specific baseline cancer rate for colorectal cancer among Saudi population.

	λ_a^s **baseline incidence rate for CRC**	
Age group	**Male (per 100,000 population)**	**Female (per 100,000 population)**
40-45	10.2	10.1
45-50	20.4	19.2
50-55	34.2	30.1
55-60	45.1	45.3
60-65	51.2	50.7
65-70	87.2	49.4
70-75	89.1	48.1
75-80	89.7	47.7

3. Results and discussion

3.1. *ERR and EAR estimates*

The risk of secondary CRC amongst patients caused by first cancer radiotherapy treatment is an area of debate in clinical radiation oncology. The biggest challenge in evaluating the second CRC risk is the latency period of onset following initial radiotherapy treatment [40, 41]. This recurrence is expected to occur many years after the first treatment [42]. This time interval between the first treatment and secondary malignancy development is the primary source of uncertainty and makes the risk difficult to be measured and impractical to test through large prospective clinical trials.

Although the ERR and EAR have the same expression, the values and interpretation of their respective parameters were different. In particular, the ERR shows a decrease with attained age, while the EAR shows a substantial increase with attained age for both males and females (Figure 1 to Figure 4). These distinct patterns were likely due to the sharp increase in baseline risks with age, as suggested by Gilbert et al. [43]. Both ERR and EAR increased with radiation dose, regardless of gender (Figures 1 and 2).

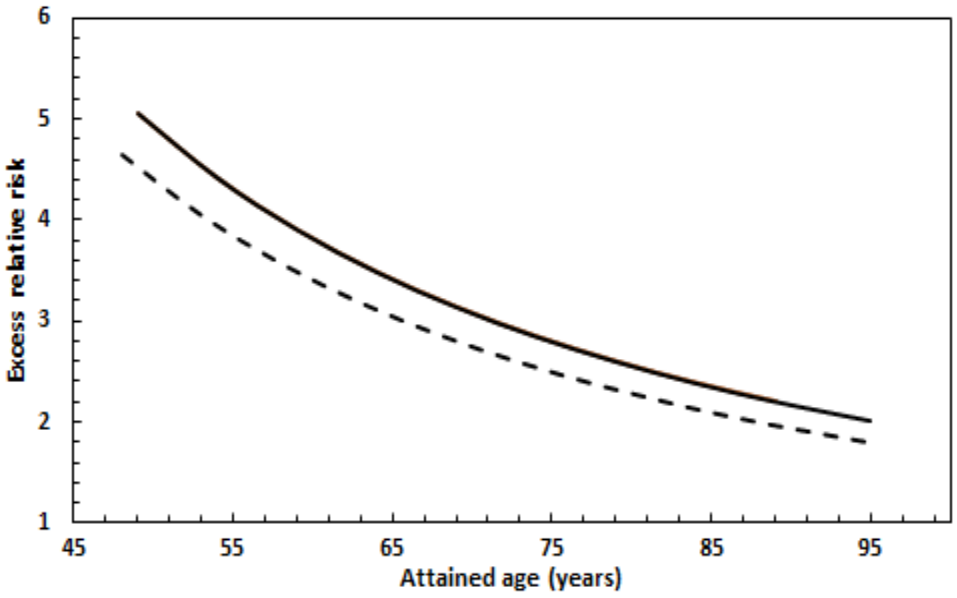

Figure 1. Excess relative risk of two male patients: age at exposure: (- - -) 43 years, irradiation dose: 45 Gy, and (—) age at exposure: 44 years, dose: 50.8 Gy.

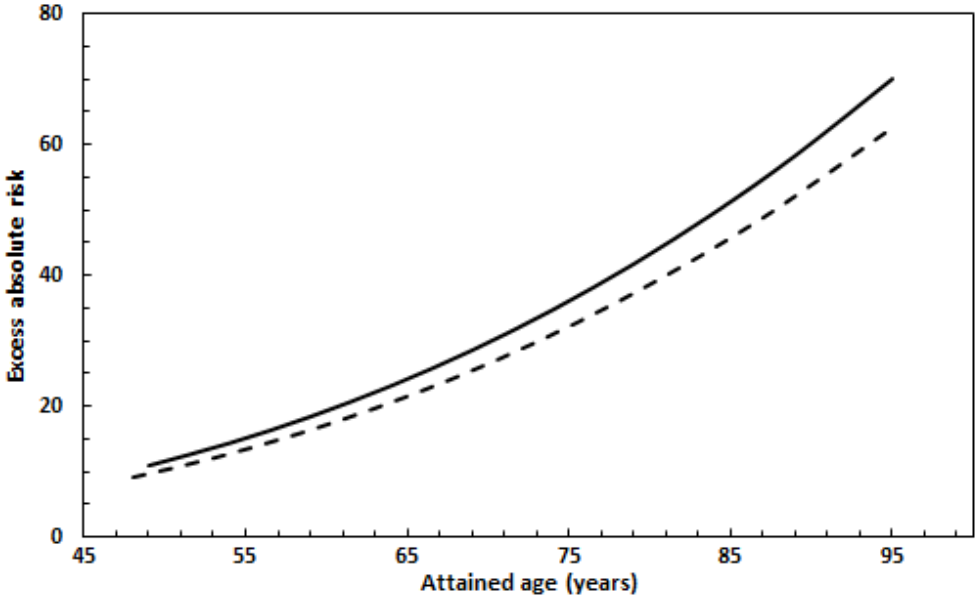

Figure 2. Excess absolute risk of two male patients: (- - -) age at exposure: 43 years, irradiation dose: 45 Gy, and (—) age at exposure: 44 years, irradiation dose: 50.8 Gy.

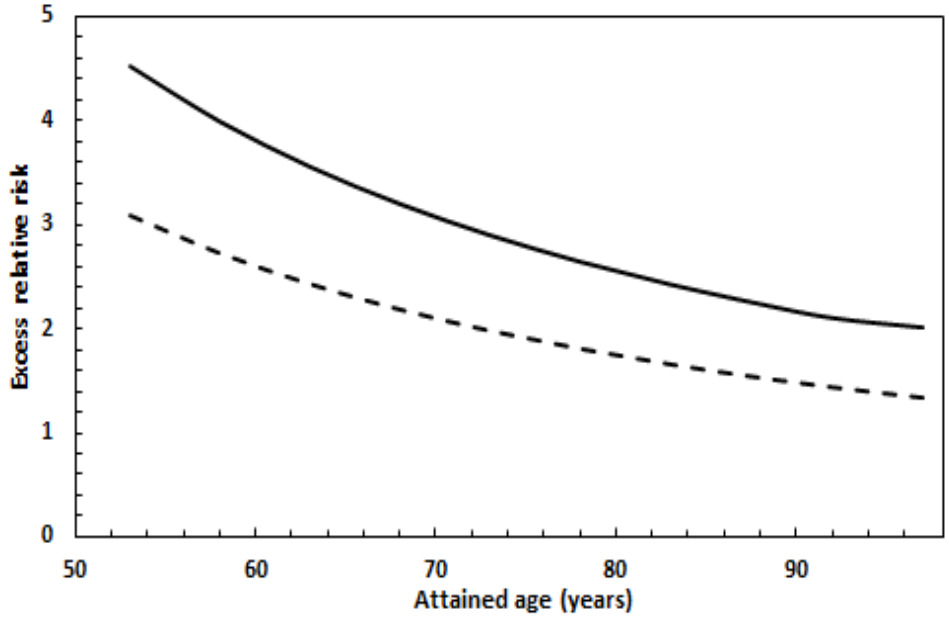

Figure 3. Excess relative risk of male (—) and female (- - -) patients with same age at exposure (48 y) and same irradiation dose (50.8 Gy).

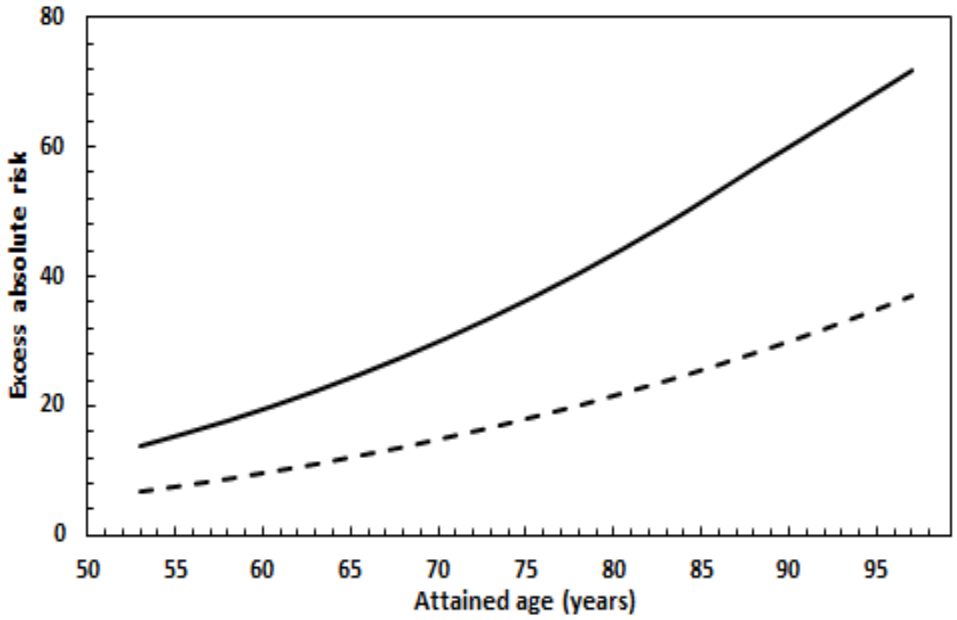

Figure 4. Excess absolute risk of male (—) and female (- - -) patients with same age at exposure (48 y) and same irradiation dose (50.8 Gy).

Our results show that both ERR and EAR estimates were higher for males than those for females (Figures 3 and 4) as affected by the CRC baseline incidence rate among the Saudi population. However, a decrease in both ERR and the EAR with increasing age at exposure is observed. In addition to the occurrence of cancer in sex-specific organs such as the prostate and ovary, growing evidence shows that CRC incidence and mortality is more predominant in males than in females. This inequality is probably due to differences in environmental exposures, estrogen level between men and women, and possibly complex interactions between these effects [44]. Women were more prone to right-sided higher severity tumor while men exhibited the tumor more on the left side [2].

For comparability purposes of the risk estimates, we computed and compared the sex-and age-specific ERR/Gy and EAR/Gy as function of attained age and age at exposure and then deducted the LAR/Gy for all genders. Although the ERR/Gy and EAR/Gy have the same expression, the values and interpretation of the factors were distinct. The ERR/Gy (which provides a convenient summary statistic) for men decreased with increasing attained age from 0.87 for exposures at the age of 43 to 0.40 for exposures at age of 59 (Figure 5(a)). However, the EAR/Gy increases with attained age but the dependence on the age at exposure was not significant (Figure 5(b)). These results were compatible with other studies [45, 46].

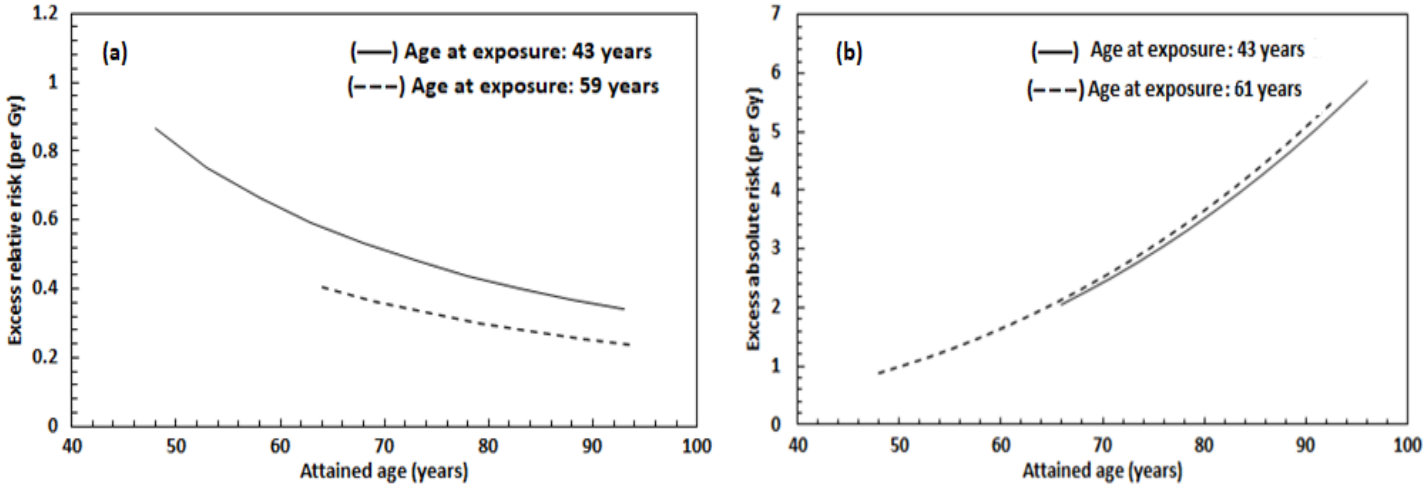

Figure 5. Age-time pattern of (a) ERR/Gy and (b) EAR/Gy vs attained age in CRC incidence associated with radiation for two male patients with different age at exposure.

As long as females patients are concerned, the ERR/Gy and the EAR/Gy decreases (Figure 6(a)) and increases respectively, (Figure 6(b)) with attained age. Again, these different patterns indicate the strong increase in baseline risks with attained age [43]. However, the dependence of the these two excess risks (namely EER/Gy and EAR/Gy) on the age at exposure was not significant as already reported by Sugiyama and coworkers [46]. For all genders, the slope of the ERR/Gy vs attained age appeared to level off at higher attained ages.

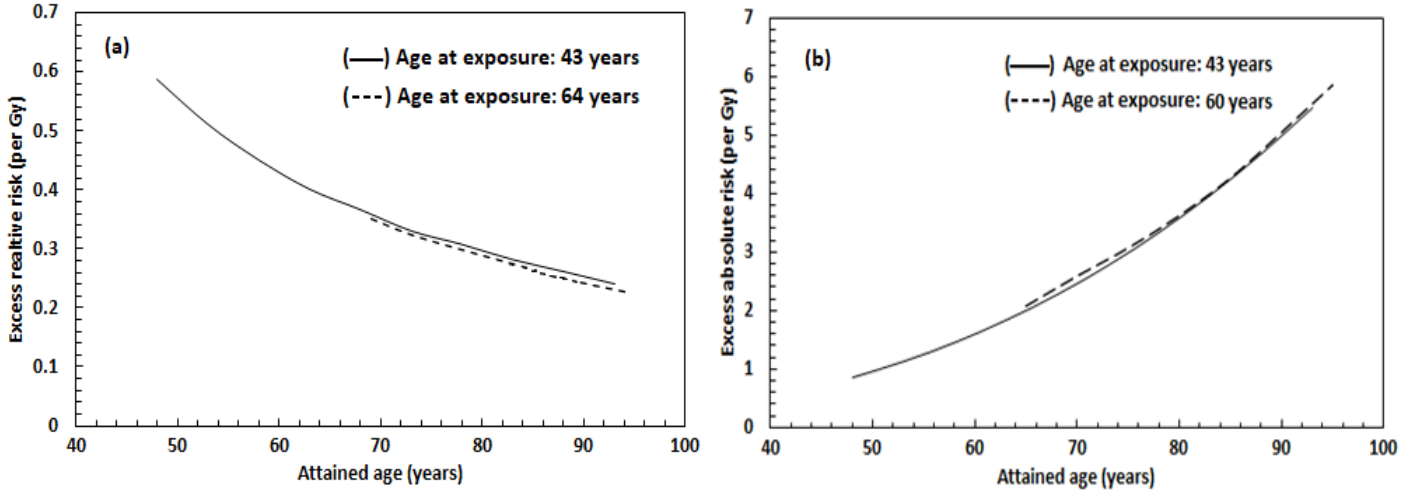

Figure 6. Age-time pattern of (a) ERR/Gy and (b) EAR/Gy vs attained age in CRC incidence associated with radiation for two female patients with different age at exposure.

Comparison between male and female patients shows that for both sex, the ERR/Gy decreased with age at exposure while EAR/Gy increased at exposure (Figures 7(a) and 7(b)). The ERR/Gy for men survivors has been found to be higher than the ERR/Gy for women (Figure 7 (a)) suggesting that men may be at an elevated risk of radiation-induced second colorectal cancer. The average male-to-female relative risk for colorectal cancer from exposure at age 0 to age 60 is 0.16 as reported by Biegon and co-workers [1]. For a given age at exposure, the EAR/Gy dependence on the age at exposure appears to not be significantly different for all genders although slightly lower among women than men. Sex-related expressed genes related to hormone metabolism may be behind the gender differences of survival rates in CRC between all genders [47].

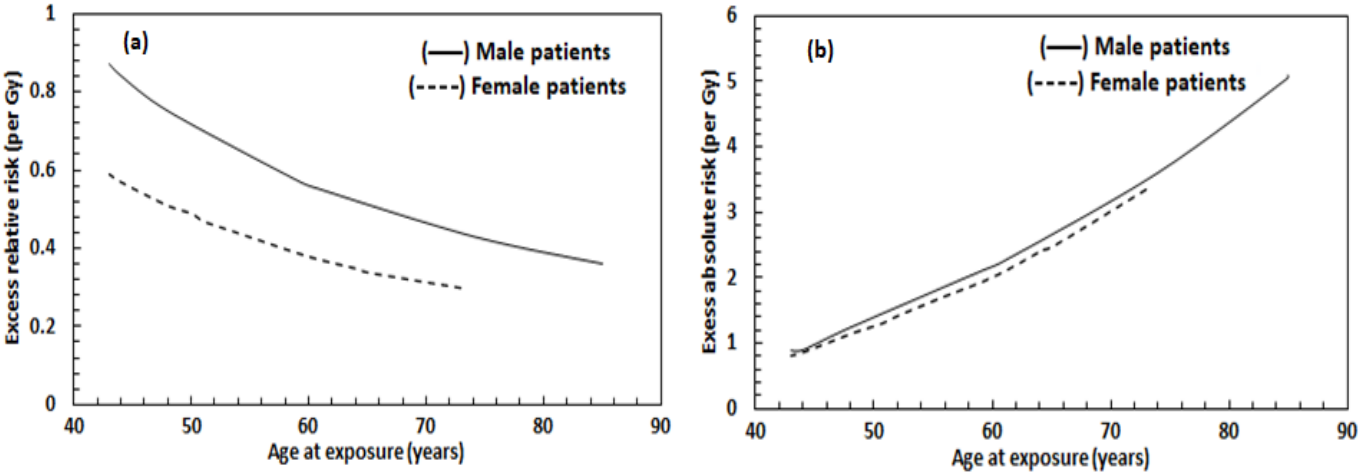

Figure 7. Age-time pattern in CRC of (a) ERR/Gy and (b) EAR/Gy incidence associated with radiation vs age at exposure for male and female patients.

3.2.LAR/Gy estimates

Being the large risk metric in second CRC risk estimates, the computation of LAR/Gy can be performed for each exposed patient, considering the parameters *s* (sex), *D* (exposure dose), *e* (age at exposure), and *a* (attained age). Alternatively, it can be computed for an exposed population considering a set of assumptions regarding genetic or environmental risk factors [38]. The first option was chosen in this study owing to the lack of genetic or environmental data of our cluster patients. Our results show that both male and female CRC survivors had an elevated LAR of developing a second cancer for all age groups, compared to the particular baseline cancer risks incidence (Tables 4 and 5). The LAR/Gy data show an inverse correlation with age at exposure with a kind of leveling off in the middle age for all genders. In female patients, more than 5-fold decrease in LAR from age at exposure of 43 to that of 73 for the same dose of 45 Gy (Figure 8). The same trend is observed

amongst male patients where for instance, 3.6-fold decrease in LAR from age at exposure of 43 to that of 74 for the same dose of 50.8 Gy (Figure 8). The higher CRC risk observed among younger patients is likely due to longer residual life expectancy and other factors, such as genetic predispositions and lifestyle risk factors. [48, 49]. However, it should be noted that the decrease in LAR for people over the age of 50 is mostly owing to other risks – as people age, they have an ever-declining chance of living long enough to develop a radiation-induced cancer.

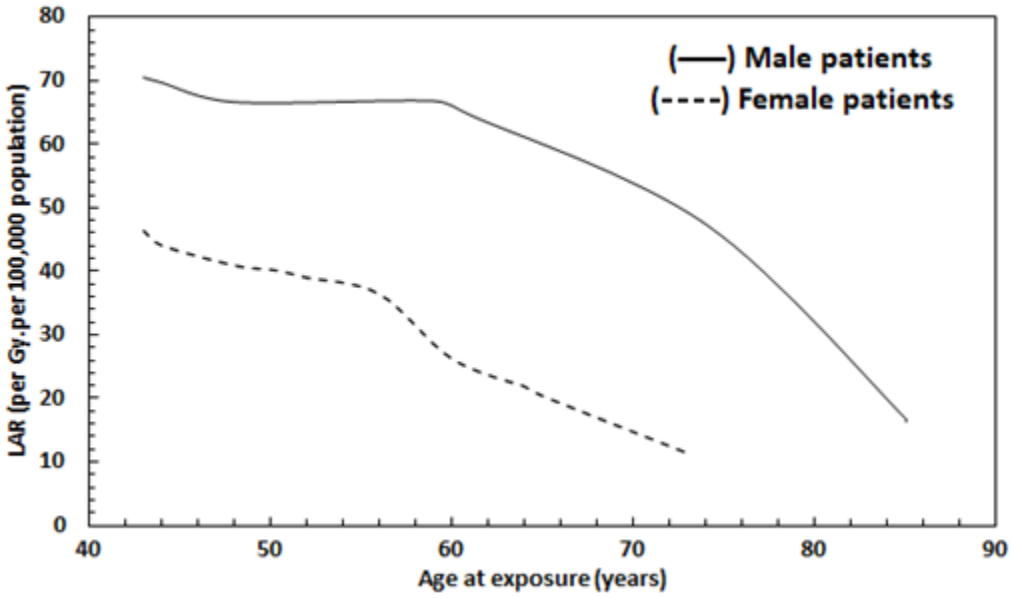

Figure 8. Age and sex-specific cumulative lifetime attributable risk vs age at exposure for CRC incidence.

These results show that females should have higher survival rates in CRC than males as already reported in many meta-analyses [50, 51] although women undergo endoscopic screening for colorectal cancer at significantly lower rates than men [52]. Across all ages, males have about a 1.5-fold higher chance of developing a second CRC than females [53]. Even though the mechanism causing these differences between males and females is not yet fully understood, the differences in fat ratios between males and females and abdominal fatness are believed to impact the risk [54, 55].

4. Conclusion

In this study, we estimated the incidence of secondary cancer recurrence resulting from external radiotherapy of primary CRC. However, applying the BEIR or any other model in predicting the occurrence of secondary radiation-induced cancer in a cancer survivor population is constrained by a lack of knowledge in some areas such as biological and genetic mechanisms at the

cellular and molecular level related to carcinogenesis, uncertainties in radiation dosimetry, partial or failure in out-patients follow-up.

The results of this study should be interpreted with caution. Despite the small sample size, our analysis highlights genderrelated differences in colorectal cancer survival rates, which may be attributed to genetic, hormonal, immunological, or environmental factors. Estimating the risk of secondary malignancies among CRC survivors following radiotherapy can help healthcare providers identify appropriate prevention strategies, keeping in mind that 20% of all cancer patients will develop recurrent tumors during their lifetime.

Ethics approval: We can confirm that this retrospective study involving patient diagnosed with CRC was approved by the Saudi National Committee on Bioethics (NCBE) in accordance with the ethical standards of the institutional and national research committee. Furthermore, informed consent obtained from each patient (or his/her legal representative) after being informed about the nature of research.

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Appendix A: Glossary

Baseline incidence rates of cancer in a given population:
Cancer incidence rate in an unexposed cohort

Excess Absolute Risk, *EAR(t)*:
Difference between incidence rates of an exposed cohort and an unexposed cohort. It designates the excess increase in incidence rate associated with radiation exposure.

$$EAR(t) = \delta_E(t) - \delta_U(t)$$

Relative Risk RR(t):
Defined as the ratio between incidence rates of an exposed and an unexposed cohort:

$$ERR(t) = \frac{\delta_E(t)}{\delta_U(t)}$$

If exposure increases the risk, then $ERR(t) > 1$; if exposure decreases the risk, then $ERR(t) < 1$, and $ERR(t) = 1$ corresponds to the case where no correlation exists between the cancer risk and the radiation exposure.

Excess Relative Risk ERR(t):
Proportion of RR(t) attributable only to radiation exposure

$$\mathrm{ERR(t)} = \mathrm{RR(t)} - 1 = \frac{\delta_E(t) - \delta_U(t)}{\delta_U(t)}$$

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تقديرات المخاطر الخبيثة الثانوية القولون والمستقيم التالية العلاج الإشعاعي: دراسة أترابية مستقبلية بين الناجين من السرطان في المملكة العربية السعودية

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المستخلص - يعد السرطان الثاني الناجم عن الإشعاع أحد الآثار الجانبية المتأخرة الحاسمة للعلاج الإشعاعي للسرطان الأول. على الرغم من أن آلية تحفيز السرطان الثانية ليست مفهومة جيدًا بعد، إلا أن العديد من العوامل ترتبط بحدوثه، مثل العمر عند التعرض، والجرعة التي يتعرض لها العضو والأنسجة المحيطة به، وطرق العلاج، والتاريخ العائلي للسرطان. تهدف هذه الدراسة إلى تقديم تقديرات طويلة المدى لحالات الإصابة بالسرطان الثاني بين الناجين من سرطان القولون في المملكة العربية السعودية. تم تحديد الخطر المنسوب مدى الحياة (LAR) بعد العلاج الإشعاعي لسرطان القولون، بين العمر عند التعرض وما يصل إلى 95 عامًا، في مجموعة مؤسسة واحدة من الناجين من السرطان من الذكور والإناث الذين كانت أعمارهم عند العلاج في حدود 43 إلى 43 عامًا. 85 سنة. تختلف تقديرات المخاطر بشكل كبير مع العمر عند التعرض والجنس وجرعة العضو.

الكلمات المفتاحية: سرطان القولون والمستقيم، العلاج الإشعاعي، جرعة، الإصابة بالسرطان للمرة الثانية، المخاطر المنسوبة مدى الحياة.