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Original Article

Lifetime Attributable Risk for Breast Cancer Induced by High-Resolution Computed Tomography During COVID-19 Pandemic

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Abstract

Objective: The widespread utilization of high-resolution computed tomography (HRCT) for diagnosing and management of COVID-19 during the pandemic has prompted worries regarding a potential rise in future breast cancer cases. We aimed to estimate the Life Attributable Risk (LAR) of breast cancer in Shiraz, Iran, linked to HRCT use during the COVID-19 pandemic.

Materials and methods: A cross-sectional study was conducted at Namazi Hospital in Shiraz from February 2, 2020, to December 31, 2022.The Imaging Performance Assessment of CT Scanners (ImPACT) patient dosimetry calculator was used to determine organ doses. LAR was computed utilizing the Biological Effects of Ionizing Radiation (BEIR) Committee models.

Results: The sample size was 666, with ages spanning from 15 to 95 years. 25% (168) had HRCT more than once (2 to 8 times). The mean and 95% uncertainty limits (UL) for Total LAR of breast cancer, considering both single and multiple doses of radiation exposure, was 217 (95% UL, 194-244) per 100,000 persons.

Conclusion: According to our research, the risk of potential breast cancer should not be overlooked. It is advised to use the ultra-low-dose protocol over the low-dose in HRCT. Physicians, pulmonologists, and infectious disease specialists are advised to avoid unnecessary and repeated requests for chest HRCT in a short period.

Keywords: Breast Cancer; High-Resolution Computed Tomography (HRCT); CT Scan; Lifetime Attributable Risk; COVID-19

Introduction

During the COVID-19 pandemic, the polymerase chain reaction (PCR) method has been utilized as the gold standard for diagnosis. However, obtaining results was time-consuming, and the test were insufficient despite low sensitivity (1-3). High-resolution computed tomography (HRCT) of the

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chest, utilized for diagnosing and managing COVID-19, became a standard tool for its availability, sensitivity, and rapid results (4-7). Most people who contracted COVID-19 underwent chest HRCT during the pandemic (8). The X-ray used in CT scans is low-dose ionizing radiation (0 to 100 milli-sieverts) and has stochastic effects. While these effects may not manifest in everyone exposed to radiation, as there is no threshold, any amount of dose can damage cells and raise the risk of cancer. In stochastic effects, cancer incidence also increases with higher doses of radiation (9, 10).

Some individuals underwent multiple CT scans, ranging from 2 to 8 scans, during the COVID-19 pandemic, which could increase the incidence rate of cancer (8, 11, 12). Some epidemiological studies have found a non-negligible increase in cancer risk from typical CT scans (13, 14). Based on a study, 0.9% of cancer cases in the US may be linked to low-dose diagnostic X-rays conducted from 1996 to 1991 (15).

According to the World Health Organization, in 2022, about 2.3 million women are expected to be diagnosed with breast cancer globally, leading to 670,000 deaths. Breast cancer was the most prevalent cancer among women in 157 of 185 countries in 2022 (16). Breast cancer is a significant health issue in Iran, representing 12.5% of all cancer cases in the country (17) and the baseline breast cancer rate is 35.5 per 100,000 individuals (18). Several risk factors have been identified for breast cancer. One of the risk factors is exposure to high-dose radiation, particularly at a young age. While exposure at any age poses risks (19-21). In a study carried out in Iran in 2023, the risk of breast cancer from chest CT was found to be 98.6 per 100,000 persons, an estimation not based on lifetime attributable risk (21).

While the association between high- and moderate-dose of ionizing radiation (above 100 mSv) and an increased risk of breast cancer is well established, the association with low-dose exposure remains incompletely understood (19). Given the widespread use of HRCT during the COVID-19 pandemic and concerns about a potential increase in cancer cases in the future in Iran, researchers decided to carry out this study. The research aims to predict the future number of potential breast cancers due to HRCT during the COVID-19 pandemic using the Excess Relative Risk (ERR), Excess Absolute Risk (EAR), and Life Attributable Risk (LAR) models put forth by the Biological Effects of Ionizing Radiation (BEIR) Committee.

Materials and methods

Data collection: A cross-sectional study was carried out at the 1000-bed Namazi Educational-Therapeutic Hospital, which is associated with Shiraz University of Medical Sciences. We selected a random sample of patients who attended Namazi Hospital as outpatients for HRCT scans or were admitted and underwent HRCT scans between 02/02/2020 and 12/31/2022, amidst the COVID-19 pandemic. To achieve this, we consulted the Statistics Center of Shiraz University of Medical Sciences and acquired data concerning the patients' age at the time of exposure (age during the CT scan), CT scan date, sex, and national ID code for all patients throughout the study period.

Dose estimation: The Philips Brilliance 16 slices and GE Light Speed 16 slices were the scanner models used. To retrieve patient dosage data, we accessed INFINITT comprehensive picture archiving and communication system (PACS) of Shiraz University of Medical Sciences. All dose-related parameters were obtained from the INFINITT PSACS system using the patient's national identification code. In cases where HRCT scans were repeated, parameters for each dose were extracted separately due to potential variations in scanning parameters. Dose parameters were sourced from the DICOM header and inputted into Microsoft Excel 2016. If a sample was diagnosed with cancer, it was replaced. Parameters included kilovoltage (KV), tube current (milliamperes) (mA), rotation time (seconds) (S), pitch factor, total collimation beam width, volume computed tomography dose index (CTDIvol in mGy), dose length product (DLP in mGy.cm), and scan length (in cm). Breast organ doses were calculated using the ImPACT patient dosimetry calculator developed by the National Radiation Protection Board of the UK.

Risk projection models: The LAR of breast cancer was calculated using the most recent projected model from the BEIR VII Committee, which was developed for low-level radiation (0–100 mGy) exposure. The model was developed using combined data, which included follow-up research on Japanese atomic bomb survivors from the Life Span Study (LSS) cohort and other medically exposed cohorts. This model is a linear no-threshold model (LNT) with a 5-year latent period for solid tissue cancers. The LAR is the probability of additional cancer risk as a result of radiation exposure, which exceeds the baseline lifetime risk (22). The EAR model was used for LAR calculation.

The BEIRE VII equations (1-4) were displayed as follows:

$$LAR_{EAR}(D, e) = \sum_{a}^{100} M(D, e, a)\, S(a) / S(e) \quad (1)$$

$$M(D, e, a) = EAR(D, e, a) \quad (2)$$

$$EAR = \beta_f \times D \times \exp[\gamma (e-25)/10]\, (a / 50)^{\eta} \quad (3)$$

The equitation (1) represents LAR for the additive model (EAR). e represents age at exposure in years. a is the attained age, in which a = e + latent period. S (a) / S (e) ratio is the surviving probability to age a, conditional on surviving to exposure age of e. In the equitation (2), M (D, e, a) is the excess absolute risk and is used to calculate LAR_{EAR}. In the equitation (3), D is the organ dose for breast in Sievert (SV), β_f is sex-specific estimates of the EAR per 10^4 Person Year-Sievert (PY-SV) for exposure age 25 and attained age 50. e represents age at exposure in years, a is attained age in years, and γ is the per-decade increase in exposure age from 0 to 30 years. η is the exponent of attained age. Details of the EAR models are represented in Table 12-2 of the BEIR VII report (9).

The breast cancer baseline rates in Iran for 2019, stratified by sex and age groups, were obtained from the IHME Institute for GBD study (18).

Data Management and Analysis: Data management, data cleaning, and descriptive statistics were conducted using Microsoft Excel 2016 and Stata 17. while the R 4.3.2 software, through the LARisk package 3(23), was employed for analytical purposes. The LARisk R package computes the lifetime attributable risk of radiation-induced cancer, utilizing the RadRAT program from the US National Cancer Institute (NCI). The RadRAT tool, available at https://radiationcalculators.cancer.gov/radrat/, estimates cancer risk from radiation exposure based on BEIR VII. By extrapolating cancer risks from Japanese atomic bomb survivors to the US population, LARisk integrates LAR project functions into batch files, offering enhanced flexibility. Users can also input baseline data (life table and baseline cancer incidence rate) to transfer risks to the interested population. Lognormal dose data was utilized in the LAR analysis. LAR estimates were computed separately for individuals with a single exposure and multiple exposures (2–8 times) due to differing exposure scenarios, followed by the calculation of the total LAR for all. Limited sample sizes in each subgroup prevented the calculation of LAR for each exposure subgroup in multiple exposure groups. For scan parameters, the median and interquartile range (IQR) were chosen for reporting due to the skewed data distribution.

Results

The age of the patients varied from 15 to 95 years old, classified into 8 groups based on ten-year increments. The average age of the patients was 50.2 ± 19.6. During the study period, 168 of 666 (25%) had HRCT more than once (between 2 and 8 times) (Table 1).

Table 1: Scan number for females during the study period

Scan No.	Total Females	Total Scans
1	498	498
2	108	216
3	39	117
4	12	48
5	4	20
6	4	24
7	0	0
8	1	8
Total	666	931

Scan parameters: Table 2 depicts the parameters used in the scan model to calculate breast organ doses for different age groups. Detector collimation for Philips, Brilliance 16 and GE Medical, Light speed 16 were 16×1.5 and 20 mm respectively. The median (IQR) for breast dose was 6 (4.1).

The mean and 95% uncertainty limits (UL) of LAR for females receiving a single dose (one time HRCT) were 220 (95% UL, 202–240) per 100,000 individuals. For females who had HRCT two or more times, the mean and 95% uncertainty limits (UL) of LAR were 210 (95% UL, 172-256) per 100,000 people in the study period. The total LAR for all doses (single and multiple) was 217 (95% UL, 194-244) per 100,000 persons. Figure 1 illustrates an estimation of the lifetime attributable risk for breast cancer per 100,000 women. This estimation is grounded in the absolute risk transfer model, which may be associated with a single exposure, categorized by age at exposure. Figure 2 presents an estimation of lifetime attributable risk based on transferring the absolute risk of breast cancer per 100,000 women associated with exposures of 2 doses or more at the age of exposure. Figure 3 shows an estimation of total LAR for breast cancer by transferring absolute risk per 100,000 women across all scans, depending on age of exposure.

Table 2: The median (IQR) value of scan parameters for each exposed age group based on scan models and age groups

	Exposed age (years)	15-24	25-34	35-44	45-54	55-64	65-74	75-84	≥ 85
Philips, Briliance 16	Kilovoltage (KV)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)
	Tube current (mA)	71 (60)	85 (82)	98 (76)	113 (91)	105 (100)	107 (98)	87 (54)	99 (102)
	Rotation time (s)	0.75 (0)	0.75 (0)	0.75 (.25)	0.75 (0)	0.75 (0)	0.75 (0)	0.75 (0.25)	0.75 (0)
	Pitch	0.81 (0.25)	0.81 (0.25)	0.81 (0.25)	0.81 (0.25)	0.81 (0.25)	0.81 (0.25)	0.81 (0.253)	0.81 (0.253)
	Scan length (mm)	285 (48)	279(36)	280 (36)	280 (45)	279 (48)	276 (45)	279.5 (60)	273.5 (33)
	CTDIvol (mGray)	3.11 (2.03)	4.58 (3.08)	4.63 (4.16)	5.78 (4.19)	5.58 (3.87)	5.9 (4.78)	4.48 (3.49)	4.75 (3.24)
	DLP(mGy.cm)	110 (60)	135 (72)	142 (105)	165 (111)	169 (126)	181 (144)	135 (101)	170 (151)
GE Medical, Light speed 16	Kilovoltage (KV)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)	120 (0)
	Tube current (mA)	117 (49)	117 (59)	147 (88)	147 (139)	147 (139)	147 (94)	147 (48)	118 (59)
	Rotation time (s)	1 (0.31)	0.69 (0.31)	0.84 (0.31)	0.87 (0.31)	0.69 (0.31)	0.69 (0.31)	1 (0.31)	1 (0.31)
	Pitch	1.75 (0)	1.75 (0)	1.75 (0)	1.75 (0)	1.75 (0)	1.75 (0)	1.75 (0)	1.75 (0)
	Scan length (mm)	255 (45)	270 (50)	270 (49)	255 (52)	265 (40)	261 (32)	267 (51)	265 (65)
	CTDIvol (mGray)	6.34 (4.05)	5.61 (4.15)	6.41 (4.43)	6.42 (8.8)	6.6 (6.46)	5.6 (5.43)	6.36 (3.51)	6.34 (3.33)
	DLP (mGy.cm)	184 (143)	182 (127)	205 (127)	192 (237)	195 (157)	174 (141)	213(128)	184 (107)

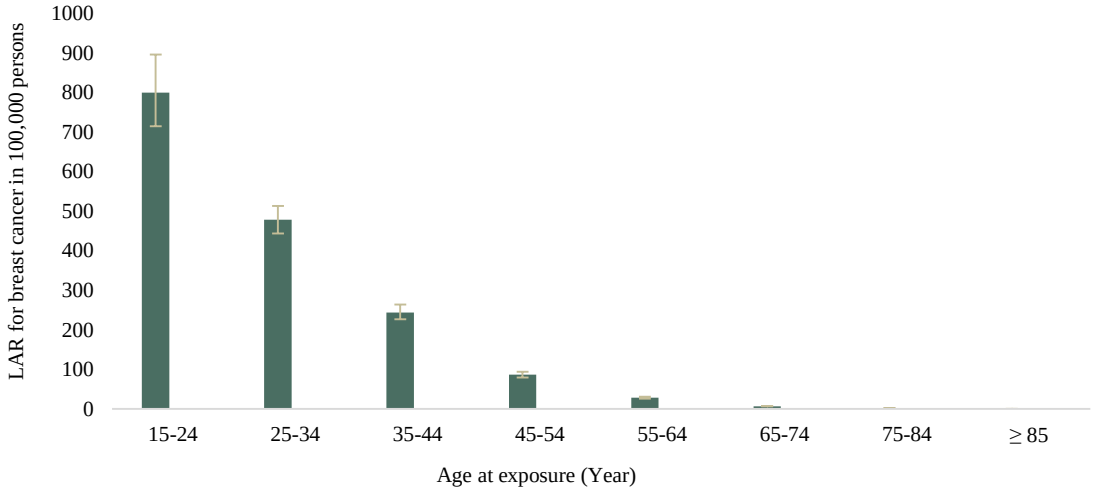

Figure 1: LAR estimates for breast cancer (mean and 95% UL) in 100,000 persons with a single exposure dose, according to age at exposure

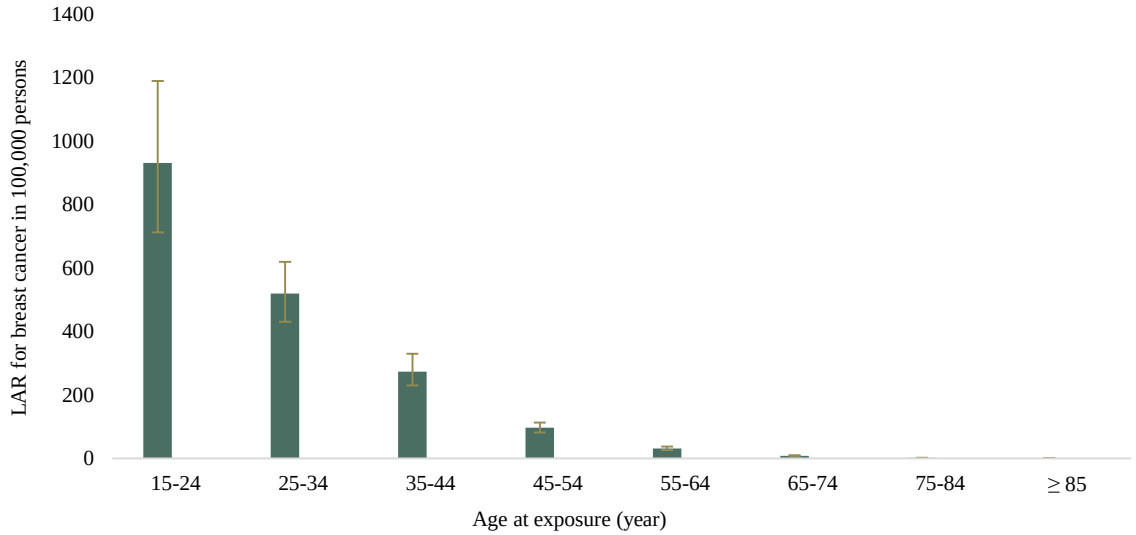

Figure 2: LAR estimates for breast cancer (mean and 95% UL) in 100,000 persons with 2 and more dose exposures, according to age at exposure

Discussion

The widespread use of HRCT for diagnosing and managing COVID-19 during the pandemic has raised concerns about a potential increase in breast cancer cases in Iran. Many studies have not been conducted on the topic of radiation exposure during CT scans and its association with cancer. BEIR Committee, responsible for investigating the biological effects of ionizing radiation, reported in 2007 that up to that date, no study had directly examined the potential cancer risk from CT scanning. However, considering the evidence from ionizing radiation studies on the LSS cohort, the cancer risk from CT scan exposure should not be overlooked (9). A study by Gonzalez et al. in 2009 found that around 1,800 (95% UL, 800 –2,300) per 100,000 females cases of breast cancer, in the US could be linked to CT scans conducted in 2007 (24).

We computed LAR estimates for breast cancer using BEIR Committee models. Our estimates suggest that around 217 (95% UL, 194 –244) per 100,000 females future breast cancer might be associated with HRCT utilization in Iran during the COVID-19 pandemic.

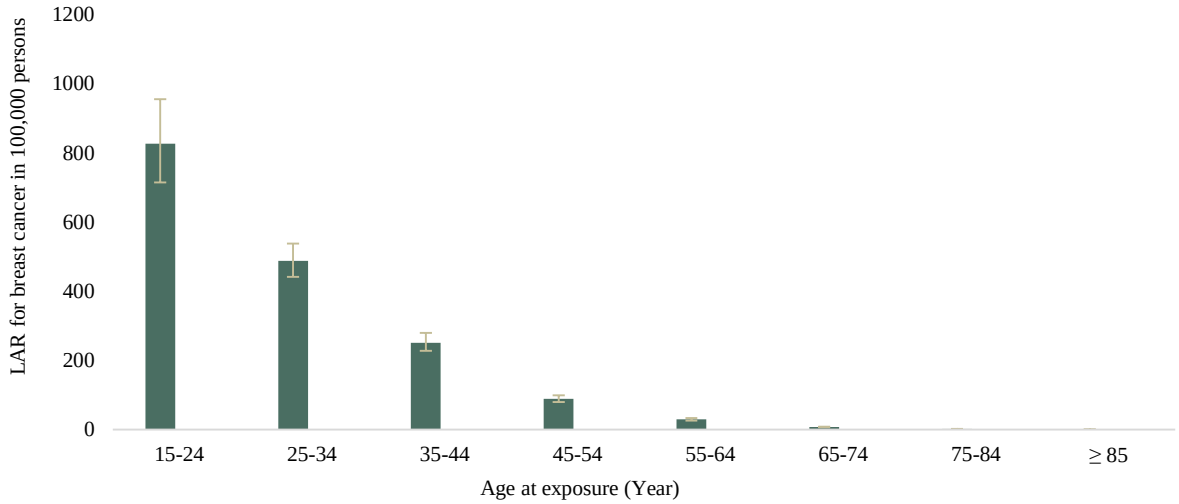

Figure 3: Total LAR estimates for breast cancer (mean and 95% UL) in 100,000 persons (for all doses), according to age at exposure

In a 2023 study in Iran to estimate the LAR of breast cancer in women who had HRCT during the COVID-19 pandemic, the median and IQR probability of LAR were 17.64 (0.88-167.95) per 100,000 women. Another study conducted in Iran in 2023 indicated that the risk of breast cancer from Chest CT scans was 98.6 per 100,000 females (not the LAR study) (25).

The BEIR committee stated in their latest report that the risk of developing cancer in life increases as the age of exposure decreases for individuals under 30 years old (9). In a 2017 study of 200 women aged 15 to 80 from the West Bank and Gaza Strip in Palestine, the lifetime attributable risk probabilities were 0.05% for young women aged 15 to 29 years and 0.001% for older women aged 60 to 79 years (26). In our study, the risk probability for women aged 15 to 34 years was 0.58%, and for those aged 65 years and above, it was 0.003%. The link between young age of exposure and higher risk of breast cancer has been robustly shown in other research as well (19, 20). Consistent with their results, our findings confirm a high risk associated with early-age exposure.

In our research, 25% of women had undergone between 2 and 8 times HRCT during the pandemic, a pattern observed in previous studies (8, 11, 12). This study showed that females with frequent exposures face a higher risk, particularly at younger ages, compared to those with just one exposure.This finding is consistent with other studies, showing that the additional risk from radiation is proportional to the radiation dose. As the radiation dose increases, the probability of risk also increases linearly (19, 20). In a retrospective analysis of individuals who underwent multiple chest scans, cancer was found in 52.8% of cases (27).

Given the limited research on CT scanning exposure, this study can offer valuable insights in this area. Furthermore, most studies didn't input baseline data (life table and baseline cancer incidence rate) in their analysis to transfer risks to the target population. Instead, they relied on the LAR results table from the BEIR study for the American population, adjusting it based on organ dose data from their own research. This study's methodology may therefore be considered more robust.

The study had some limitations. The uncertainties associated with estimating the LAR model, like the overestimation of cancer risk at low doses prevalent in X-ray diagnostics which are detailed in the BEIR VII report. The uncertainty regarding dose estimation is another limitation of this study. For this reason, in these studies, the estimation point should not be reported alone and should be reported along with the uncertainty that was presented in this study.

Conclusion

The LAR estimates in this study suggest that the risk of HRCT should not be overlooked. Given the current use of a low-dose protocol for HRCT, it seems that implementing an ultra-low-dose protocol could serve as a beneficial preventive measure. Also avoiding unnecessary and multiple HRCT scans in patients is recommended. Some patients in this study underwent multiple HRCTs in a brief timeframe either at the physician's request or the patient's insistence due to disease-related anxiety.

Conflict of Interests

Authors declare no conflict of interests.

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The Research Ethics Committee of Schools of health and Nutrition of Shiraz University of Medical Sciences (Code: IR.SUMS.SCHEANUT.REC.1401.119) reviewed and approved the study protocol.

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