JAMA Surgery | Original Investigation

Risk of Hematologic Malignant Neoplasms From Abdominopelvic Computed Tomographic Radiation in Patients Who Underwent Appendectomy

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IMPORTANCE Whether computed tomography (CT) radiation is truly carcinogenic remains controversial. Large epidemiological studies that purportedly showed an association between CT radiation and carcinogenesis were limited by confounding by indication and reverse causation, because the reasons for CT examination were unknown.

OBJECTIVE To measure the risk of hematologic malignant neoplasms associated with perioperative abdominopelvic CT radiation among patients who underwent appendectomy for acute appendicitis.

DESIGN, SETTING, AND PARTICIPANTS This nationwide population-based cohort study used the National Health Insurance Service claims database in South Korea to assess 825 820 patients who underwent appendectomy for appendicitis from January 1, 2005, to December 31, 2015, and had no underlying risk factors for cancer. Patients were divided into CT-exposed (n = 306 727) or CT-unexposed (n = 519 093) groups. The study was terminated on December 31, 2017, and data were analyzed from October 30, 2018, to September 27, 2020.

EXPOSURES Perioperative abdominopelvic CT examination from 7 days before to 7 days after appendectomy.

MAIN OUTCOMES AND MEASURES The primary outcome was the incidence rate ratio (IRR) of hematologic malignant neoplasms for both groups. The secondary outcomes were IRR of abdominopelvic organ cancers and IRR of all cancers. The lag period was 2 years for the primary outcome and 5 years for secondary outcomes. The IRRs were calculated using Poisson regression models with adjustment for age and sex.

RESULTS Among the study population of 825 820 patients (52.9% male; median age, 28 [interquartile range, 15-41] years), hematologic malignant neoplasms developed in 323 patients in the CT-exposed group during 1 486 518 person-years and 500 patients in the CT-unexposed group during 3 422 059 person-years. For all hematologic malignant neoplasms, the IRR for the CT-exposed vs CT-unexposed group was 1.26 (95% CI, 1.09-1.45; P = .002). In terms of individual categories of hematologic malignant neoplasms, the CT-exposed group had an elevated risk only for leukemia (IRR, 1.40 [98.75% CI, 1.04-1.87, adjusted by Bonferroni correction]; P = .005). There was no between-group difference in incidence rate of abdominopelvic organ cancers (IRR, 1.07 [95% CI, 1.00-1.15]; P = .06) and that of all cancers (IRR, 1.04 [95% CI, 0.99-1.09]; P = .14).

CONCLUSIONS AND RELEVANCE This study controlled for reverse causation bias by defining the reasons for CT scan, and findings suggest that abdominopelvic CT radiation is associated with a higher incidence of hematologic malignant neoplasms. Efforts should be continued for judicious use of CT examinations.

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JAMA Surg. 2021;156(4):343-351. doi:10.1001/jamasurg.2020.6357
Published online January 20, 2021.

Whether computed tomographic (CT) radiation really induces cancers remains controversial.[1-3] At least in children and adolescents, the association between CT radiation and carcinogenesis seems plausible given the supporting results of multiple large epidemiological studies.[4-8] However, inclusion criteria of these studies were vague, lacking information regarding the reasons for the CT scan. The reported carcinogenic risks may have been overestimated because previous studies[4-8] had potential biases, including confounding by indication (CT examination was performed because of a predisposing factor) and reverse causation (preexisting but undetectable malignant neoplasms as the reasons for the CT scan).[1,2,9] Indeed, other studies showed that such biases might lead to overestimation of the carcinogenic risk.[10-12]

Patients with acute appendicitis make up a very relevant target population for the investigation of the carcinogenic risk of CT. First, most of these patients are children and young adults who have normal life expectancies and are more vulnerable to radiation-induced carcinogenesis than older patients. Second, CT is increasingly used in patients with suspected appendicitis.[13-15] Third, appendicitis is a very common benign disease with a reported incidence of 100 to 206 per 100 000 person-years.[16] Even if the carcinogenic risk of CT is very small, the risk in such a large number of exposed patients may lead to a measurable number of excess cancers.

Because red bone marrow is among the most radiosensitive tissues,[4,17] the carcinogenic risk of hematologic malignant neoplasms from ionizing radiation has been of particular concern. In addition, more than 10% of whole-body red bone marrow is distributed in os coxae, which is covered by abdominopelvic CT.[18] We aimed to assess the risk of hematologic malignant neoplasms after perioperative abdominopelvic CT in patients who underwent appendectomy for appendicitis in South Korea.

Key Points

Question Is there a risk of hematologic malignant neoplasms from abdominopelvic computed tomography (CT) radiation when reverse causation bias is controlled for by defining the reasons for CT scan?

Findings In this nationwide population-based cohort study that included 825 820 patients who underwent appendectomy for acute appendicitis, there was a substantial excess risk of hematologic malignant neoplasms in the CT-exposed group compared with the CT-unexposed group. The carcinogenic risk was most pronounced in patients aged 0 to 15 years.

Meaning In this study, perioperative abdominopelvic CT was associated with a higher incidence of hematologic malignant neoplasms.

Methods

Study Design and Setting

This nationwide population-based cohort study was conducted in South Korea.[19] This study was exempted from ethical approval by the institutional review board of Seoul National University Bundang Hospital because the database was publicly released for academic purposes and did not include patient identifiers. This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[20] and Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD)[21] guidelines.

We used the claims database from the National Health Insurance Service of South Korea, which administers a single-payer health care system. Because physicians have to claim reimbursement to the National Health Insurance Service for most medical procedures, the database encompasses comprehensive information regarding patient demographics, diagnoses, medical institutions, claims for medical procedures, and prescriptions. The diagnoses are coded using the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*). The National Health Insurance Service database includes medical information of the nearly entire population (97%) from 2002 to 2005 and that of the entire population since 2006.

Patients

We included patients who underwent appendectomy for appendicitis (acute appendicitis [*ICD-10* code K35]; other appendicitis [*ICD-10* code K36]; and unspecified appendicitis [*ICD-10* code K37]) from January 1, 2005, to December 31, 2015. Each patient entered the cohort on the date of appendectomy and exited from the cohort if any of the following occurred: study termination (December 31, 2017), death, or documentation of any hematologic malignant neoplasm.

We then excluded patients with other risk factors of carcinogenesis. First, we excluded patients who had documented cancers (*ICD-10* codes C00-C97, D45-D46, D47.1, and D47.3-D47.5) before appendectomy. Second, we excluded patients who had documented diseases or syndromes that predispose patients to have cancers (eTable 1 in the Supplement).[10,12] Third, we excluded those who had documentation of CT examinations performed more than 7 days before appendectomy. Fourth, we excluded patients whose diagnosis was changed to appendiceal cancer after appendectomy. Finally, we excluded patients whose follow-up duration was shorter than our predefined lag period, including those who developed any cancer during the lag period. Because the carcinogenic effect of radiation is not immediate after exposure, we assumed that cancers detected during the lag period were not attributable to the CT radiation. We set the lag period as 2 years[4,7] for our primary analysis.

CT Exposure

We divided the patients into a CT-exposed or CT-unexposed group according to the presence of claim codes of abdominopelvic CT conducted from 7 days before to 7 days after appendectomy. We set the 7-day threshold in consideration of the potential delay between CT and appendectomy and the use of CT for postoperative evaluation of surgical complications. In the primary analysis, we did not count CT exposure after more than 7 days since appendectomy. We accounted for such CT exposure in the subgroup analysis and ad hoc analysis.

Because individual dosimetry data were not available, we estimated the dose from abdominopelvic CT on red bone marrow using the Korean survey data[22,23] and dose coefficients for abdominopelvic CT (eMethods and eTable 2 in the Supplement).[24] Based on our calculation, the mean dose on red bone marrow was 14.7 mGy.

Outcomes

We set our primary outcome as the occurrence of any hematologic malignant neoplasm for the following reasons. First, abdominopelvic CT generally results in higher radiation exposure for red bone marrow, which is more radiosensitive than other body parts.[5,25] Second, uncertainty remains regarding which category of hematologic malignant neoplasms is associated with CT radiation. Previous studies showed conflicting results even for leukemia, which is the most acknowledged radiation-induced hematologic malignant neoplasm.[4-8,10-12] Uncertainty also exists for lymphoma or myelodysplastic syndromes.[4,5,8,10-12,26,27] Therefore, we set all hematologic malignant neoplasms collectively as the primary outcome and then analyzed individual categories to determine which category contributes to excess risk.

We collected hematologic malignant neoplasms, including lymphoma (*ICD-10* codes C81-C88), multiple myeloma (*ICD-10* code C90), leukemia (*ICD-10* codes C91-C96), and myelodysplastic syndromes and others (*ICD-10* codes D45-D46, D47.1, and D47.3-D47.5) as documented as the primary diagnosis during hospitalization in the National Health Insurance Service database. It was a uniform practice pattern in the catchment area that patients with malignant neoplasms were admitted to hospitals, during which time they were assigned the primary diagnosis codes. These primary diagnosis codes have been used in many other studies[28,29] and cross-validated against the national cancer registry database.[30] If a patient had multiple different diagnosis codes of hematologic malignant neoplasms, we chose the most frequently documented diagnosis code in each patient. We prioritized a code for a specific disease over a code for unspecified disease or disease not otherwise specified.

Secondary outcomes were the occurrence of any abdominopelvic organ cancers and that of all cancers. Abdominopelvic organ cancers included any malignant neoplasms of the digestive organs (*ICD-10* codes C15-C26), female genital organs (*ICD-10* codes C51-C58), male genital organs (*ICD-10* codes C60-C63), or urinary tract organs (*ICD-10* codes C64-C68). All cancers included any malignant neoplasm (*ICD-10* codes C00-C97, D45-D46, D47.1, and D47.3-D47.5). For the secondary outcomes, we set the lag period as 5 years[4] and used documentation of abdominopelvic organ cancers or any cancer, as appropriate, as criteria for cohort exit instead of hematologic malignant neoplasms.

Statistical Analysis

Data were analyzed from October 30, 2018, to September 27, 2020. We measured the incidence rate ratios (IRRs) for the primary and secondary outcomes between the CT-exposed and CT-unexposed groups. Accrual of person-years began 2 years after the appendectomy (ie, lag period) for the primary outcome and 5 years after the appendectomy for the secondary outcomes. We calculated the IRRs using Poisson regression with an offset for person-years. We adjusted for age at the time of appendectomy and sex and added an interaction term between age and sex. We calculated *P* values using the likelihood ratio test comparing 2 Poisson regression models with and without the CT exposure status. In addition, we stratified IRRs by the number of years since exposure to evaluate a trend in IRRs according to time. We also calculated the number of excess cancers and absolute excess incidence rate in the CT-exposed group.[5]

We performed 2 sensitivity analyses. First, we varied the lag period from 6 months to 5 years. Second, we adjusted for other potential confounders (year of appendectomy, hospital setting, and insurance premium [reflecting economic status]) in addition to age and sex.

We performed subgroup analyses for all collective hematologic malignant neoplasms by including corresponding interaction terms in the model. We defined the subgroups by age, sex, year of appendectomy, hospital setting, insurance premium at the time of appendectomy, and subsequent CT examinations performed after more than 7 days since appendectomy. Age and sex are well-known factors that affect cancer incidence.[31] Other variables were assumed to be associated with cancer incidence.

We performed ad hoc analyses by the number of CT examinations per patient, regardless of the group assignment in the primary analysis. In counting the number of CT examinations, we included periappendectomy CT and subsequent CT examinations that were performed at least 2 years (ie, lag period) before the cohort exit. For each patient, the numbers of abdominopelvic and any CT examinations were counted. We tested for a linear trend in incidence rate according to the number of CT examinations (continuous variable) using Poisson regression models. When calculating the IRRs, patients were regrouped according to the number of CT examinations (categorical variable of 0, 1, or ≥2). The detailed method of person-year calculation is illustrated in the eFigure in the Supplement.[11]

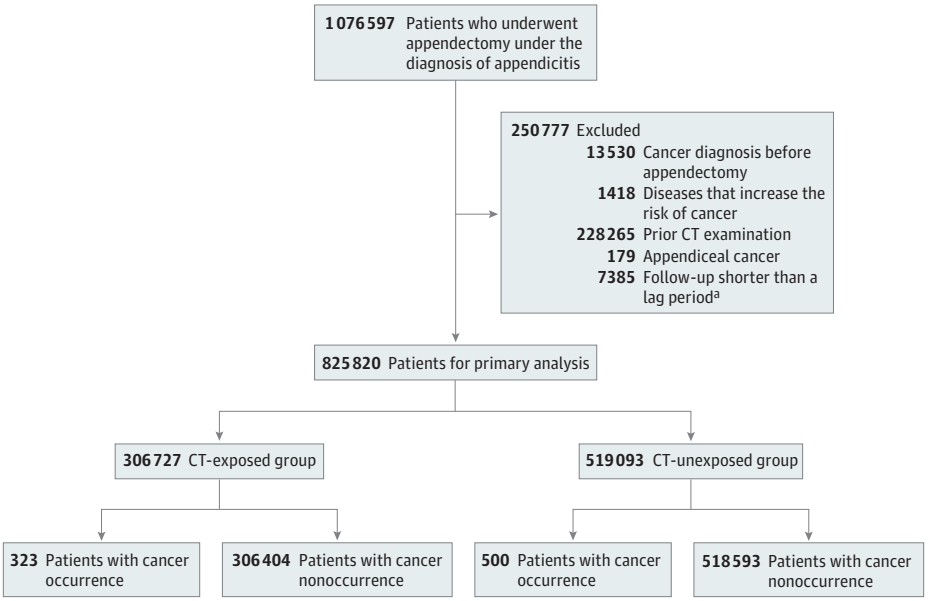
A 2-sided $P < .05$ indicated statistical significance. For testing the 4 predefined categories of hematologic malignant neoplasms (lymphoma, multiple myeloma, leukemia, and myelodysplastic syndromes), we applied a Bonferroni-corrected significance level of .0125 and calculated 98.75% CIs. Statistical analyses were performed using Stata statistical software, version 15.0 (StataCorp LLC).

Results

Patients

We identified 1 076 597 patients who underwent appendectomy for appendicitis. We excluded 250 777 patients to minimize confounding bias, as described earlier. The primary analysis included 825 820 patients (median age, 28 [interquartile range, 15-41] years) (**Figure 1**), including 437 219 male (52.9%) and 388 601 female (47.1%) patients. The CT-exposed group included 306 727 patients and the CT-unexposed group included 519 093 (**Table 1**). The median duration of follow-up af-

Figure 1. Study Flow Diagram



[a] Varied in the sensitivity analysis.

Table 1. Characteristics of Study Population by CT Exposure Status[a]

Variable	Patient group				
		CT-exposed group		CT-unexposed group	
	All, No. (%) (n = 825 820)	No. (%) of patients (n = 306 727)	No. of hematologic malignant neoplasms (n = 323)	No. (%) of patients (n = 519 093)	No. of hematologic malignant neoplasms (n = 500)
Sex					
Male	437 219 (52.9)	163 298 (53.2)	204	273 921 (52.8)	290
Female	388 601 (47.1)	143 429 (46.8)	119	245 172 (47.2)	210
Age at the study entry, y					
0-15	183 119 (22.2)	54 324 (17.7)	30	128 795 (24.8)	45
16-30	262 460 (31.8)	96 388 (31.4)	37	166 072 (32.0)	74
31-45	209 484 (25.4)	83 793 (27.3)	64	125 691 (24.2)	89
46-60	113 134 (13.7)	47 196 (15.4)	72	65 938 (12.7)	127
>60	57 623 (7.0)	25 026 (8.2)	120	32 597 (6.3)	165
Year of appendectomy					
2005-2008	353 259 (42.8)	72 762 (23.7)	151	280 497 (54.0)	381
2009-2012	299 103 (36.2)	153 560 (50.1)	148	145 543 (28.0)	100
2013-2015	173 458 (21.0)	80 405 (26.2)	24	93 053 (17.9)	19
Hospital setting					
Tertiary/secondary hospital	597 664 (72.4)	272 574 (88.9)	290	325 090 (62.6)	338
Primary clinic	228 156 (27.6)	34 153 (11.1)	33	194 003 (37.4)	162
Insurance premium, quartile[b]					
First	139 036 (16.8)	47 366 (15.4)	48	91 670 (17.7)	93
Second	171 026 (20.7)	60 405 (19.7)	65	110 621 (21.3)	89
Third	206 152 (25.0)	77 320 (25.2)	70	128 832 (24.8)	125
Fourth	242 044 (29.3)	101 308 (33.0)	119	140 736 (27.1)	135
Missing	67 562 (8.2)	20 328 (6.6)	21	47 234 (9.1)	58

Abbreviation: CT, computed tomography.

[a] Because of rounding, percentages may not total 100.

[b] Reflects level of income. The first quartile indicates the population with the lowest income.

ter appendectomy was 8.2 (interquartile range, 5.4-10.6) years. There was an obvious increase in periappendectomy abdominopelvic CT use during the study period from 9513 of 89 032 patients (10.7%) in 2005 to 23 691 of 52 516 (45.1%) in 2015.

Hematologic malignant neoplasms developed in 823 patients during 4 908 577 person-years of follow-up: 323 patients during 1 486 518 person-years in the CT-exposed group, and 500 patients during 3 422 059 person-years in the

Table 2. Number of Cancers and IRRs

Outcome	Patient group, No. of cancers		IRR (95% CI)[a]	No. of excess cancers in CT-exposed group[a,b]	Absolute excess incidence rate per 100 000 person-years (95% CI)[a,c,d]
	CT-exposed (n = 306 727)	CT-unexposed (n = 519 093)			
Primary[e]					
Hematologic malignant neoplasms	323	500	1.26 (1.09 to 1.45)[f]	66[g]	4.44 (1.83 to 6.70)
Lymphoma (*ICD-10* codes C81-C88)[h]	116	199	1.13 (0.84 to 1.51)	13	0.90 (−1.46 to 2.65)
Multiple myeloma (*ICD-10* code C90)[h]	41	54	1.31 (0.78 to 2.21)	10	0.66 (−0.77 to 1.51)
Leukemia (*ICD-10* codes C91-C96)[h]	125	185	1.40 (1.04 to 1.87)[i]	35	2.38 (0.35 to 3.90)
Myelodysplastic syndromes and others (*ICD-10* codes D45-D46, D47.1, D47.3-D47.5)[h]	41	62	1.21 (0.73 to 2.01)	7	0.49 (−1.00 to 1.39)
Secondary[j]					
Abdominopelvic organ cancers	1152	2420	1.07 (1.00 to 1.15)	76	11.08 (−0.43 to 21.80)
All cancers					
Excluding hematologic malignant neoplasms	2173	5022	1.02 (0.97 to 1.07)	44	6.51 (−9.80 to 22.01)
Including hematologic malignant neoplasms	2338	5323	1.04 (0.99 to 1.09)	85	12.44 (−4.23 to 28.32)

Abbreviations: CT, computed tomography; *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*; IRR, incidence rate ratio.

[a] Adjusted for age and sex.

[b] The excess number of cancers attributed to abdominopelvic CT radiation exposure in the exposed group was calculated as [1 − (1/IRR)] times the observed number of cancers in the exposed group.

[c] The excess number of cancers was divided by the total number of person-years of the exposed group to estimate the absolute excess incidence rate in the exposed group compared with the unexposed group.

[d] Because the absolute excess incidence rate was derived using the IRR estimate, its 95% CI was obtained similarly using the uppermost and lowermost values of the 95% CI of the IRR.

[e] Analyzed based on a 2-year lag period.

[f] Statistically significant at 2-sided $P < .05$.

[g] Because of rounding, the total number of excess cancers is not equal to the sum of the subcategories.

[h] 98.75% CIs were calculated to adjust for multiple testing using Bonferroni correction.

[i] Statistically significant at 2-sided $P < .0125$.

[j] Analyzed based on a 5-year lag period.

CT-unexposed group. In the CT-exposed group, leukemia was most common (n = 125), followed by lymphoma (n = 116), myelodysplastic syndromes and others (n = 41), and multiple myeloma (n = 41). In the CT-unexposed group, lymphoma was most common (n = 199), followed by leukemia (n = 185), myelodysplastic syndromes and others (n = 62), and multiple myeloma (n = 54).

Carcinogenic Risk of CT Radiation

For all hematologic malignant neoplasms, the IRR for the CT-exposed vs CT-unexposed group was 1.26 (95% CI, 1.09-1.45; $P = .002$) (**Table 2**). An excess of hematologic malignant neoplasms began to increase approximately 3 years after CT exposure (**Figure 2**). Sixty-six excess hematologic malignant neoplasms developed in the CT-exposed group. The absolute excess incidence rate for all hematologic malignant neoplasms was 4.44 (95% CI, 1.83-6.70) per 100 000 person-years at risk.

In terms of individual categories of hematologic malignant neoplasms, the CT-exposed group had an elevated risk for leukemia (IRR, 1.40 [98.75% CI, 1.04-1.87]; $P = .005$), but not for lymphoma (IRR, 1.13 [98.75% CI, 0.84-1.51]; $P = .30$), multiple myeloma (IRR, 1.31 [98.75% CI, 0.78-2.21]; $P = .19$), or myelodysplastic syndromes and others (IRR, 1.21 [98.75% CI, 0.73-2.01]; $P = .34$). An excess of leukemia began to increase 2 to 3 years after CT exposure (Figure 2). The absolute excess incidence rate for leukemia was 2.38 (98.75% CI, 0.35-3.90) per 100 000 person-years at risk. Most of the excess hematologic malignant neoplasms were leukemia (n = 35), particularly myeloid leukemia (n = 23). The IRRs for subcategories of lymphoma and leukemia are shown in eTable 3 in the Supplement. There was no between-group difference in the incidence rate of abdominopelvic organ cancers (IRR, 1.07 [95% CI, 1.00-1.15]; $P = .06$) and that of all cancers (IRR, 1.04 [95% CI, 0.99-1.09]; $P = .14$).

Sensitivity Analyses

The results of sensitivity analyses were similar to those of the primary analysis. When the lag period was set as 6 months, the IRR for hematologic malignant neoplasms was 1.20 (95% CI, 1.05-1.36); as 1 year, 1.20 (95% CI, 1.05-1.36); as 3 years, 1.31 (95% CI, 1.13-1.53); and as 5 years, 1.34 (95% CI, 1.11-1.62) (eTable 4 in the Supplement). When the year of appendectomy, hospital setting, and insurance premium were adjusted, the IRR was 1.25 (95% CI, 1.07-1.46) (eTable 5 in the Supplement).

Subgroup Analyses

The increase in IRR for hematologic malignant neoplasms was most pronounced in patients aged 0 to 15 years (2.14 [95% CI, 1.35-3.40]) on visual inspection of forest plots (**Figure 3**), although the interaction between CT exposure and age was not significant ($P = .10$). Otherwise, there was no substantial heterogeneity across the subgroups of sex, year of appendectomy, hospital setting, insurance premium, and subsequent CT examinations ($P > .05$ for interaction) (Figure 3).

Ad Hoc Analyses

There was a tendency for the incidence rate to increase with the number of abdominopelvic CT examinations ($P = .005$ for

Figure 2. Forest Plots for Incidence Rate Ratios (IRRs) of Hematologic Malignant Neoplasms by Time Since Computed Tomography (CT) Radiation Exposure

A All hematologic malignancies

Time since CT exposure, y	IRR (95% CI)
2-3	1.02 (0.72-1.44)
3-4	1.69 (1.16-2.48)
4-5	1.17 (0.80-1.73)
5-6	1.51 (1.05-2.17)
6-7	1.33 (0.87-2.03)
7-8	1.77 (1.07-2.90)
8-9	0.99 (0.59-1.64)

B Lymphoma

Time since CT exposure, y	IRR (95% CI)
2-3	0.63 (0.32-1.24)
3-4	1.36 (0.75-2.46)
4-5	1.29 (0.72-2.33)
5-6	1.15 (0.64-2.07)
6-7	1.50 (0.76-2.99)
7-8	1.49 (0.67-3.33)
8-9	0.49 (0.14-1.72)

C Multiple myeloma

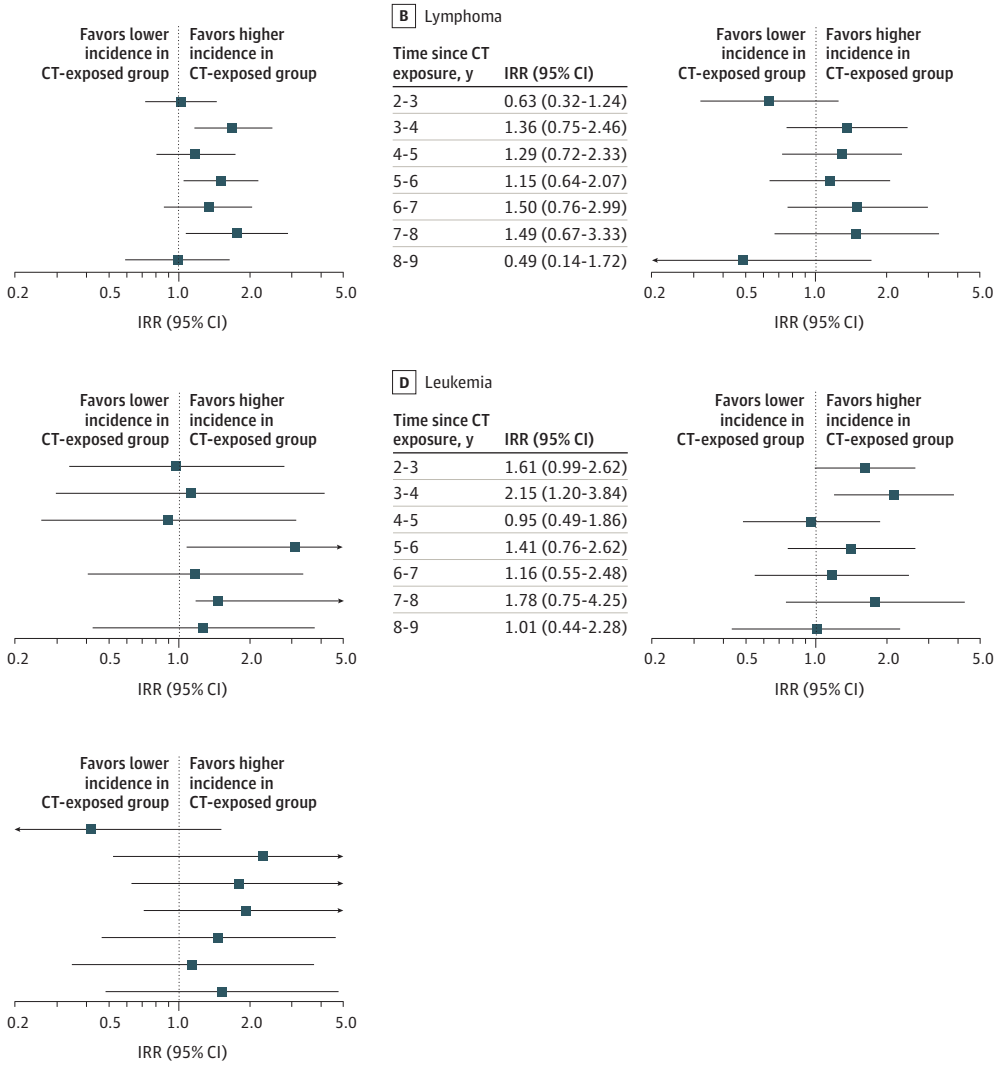
Time since CT exposure, y	IRR (95% CI)
2-3	0.98 (0.34-2.81)
3-4	1.12 (0.30-4.19)
4-5	0.90 (0.26-3.18)
5-6	3.13 (1.08-9.08)
6-7	1.17 (0.41-3.38)
7-8	9.58 (1.18-77.47)
8-9	1.27 (0.43-3.78)

D Leukemia

Time since CT exposure, y	IRR (95% CI)
2-3	1.61 (0.99-2.62)
3-4	2.15 (1.20-3.84)
4-5	0.95 (0.49-1.86)
5-6	1.41 (0.76-2.62)
6-7	1.16 (0.55-2.48)
7-8	1.78 (0.75-4.25)
8-9	1.01 (0.44-2.28)

E Myelodysplasia and others

Time since CT exposure, y	IRR (95% CI)
2-3	0.42 (0.12-1.51)
3-4	2.28 (0.53-9.85)
4-5	1.79 (0.63-5.13)
5-6	1.92 (0.71-5.18)
6-7	1.47 (0.47-4.60)
7-8	1.14 (0.35-3.75)
8-9	1.53 (0.49-4.78)



Data are given as IRRs of all hematologic malignant neoplasms (A) and by cancer subtype (B-E). Arrows in panels B, C, and E indicate that the 95% CI extends beyond the Figure boundary.

linear trend). The IRRs for hematologic malignant neoplasms were 1.21 (95% CI, 1.05-1.41) in patients with 1 abdominopelvic CT examination and 1.60 (95% CI, 1.24-2.08) in patients with at least 2 abdominopelvic CT examinations (eTable 6 in the Supplement).

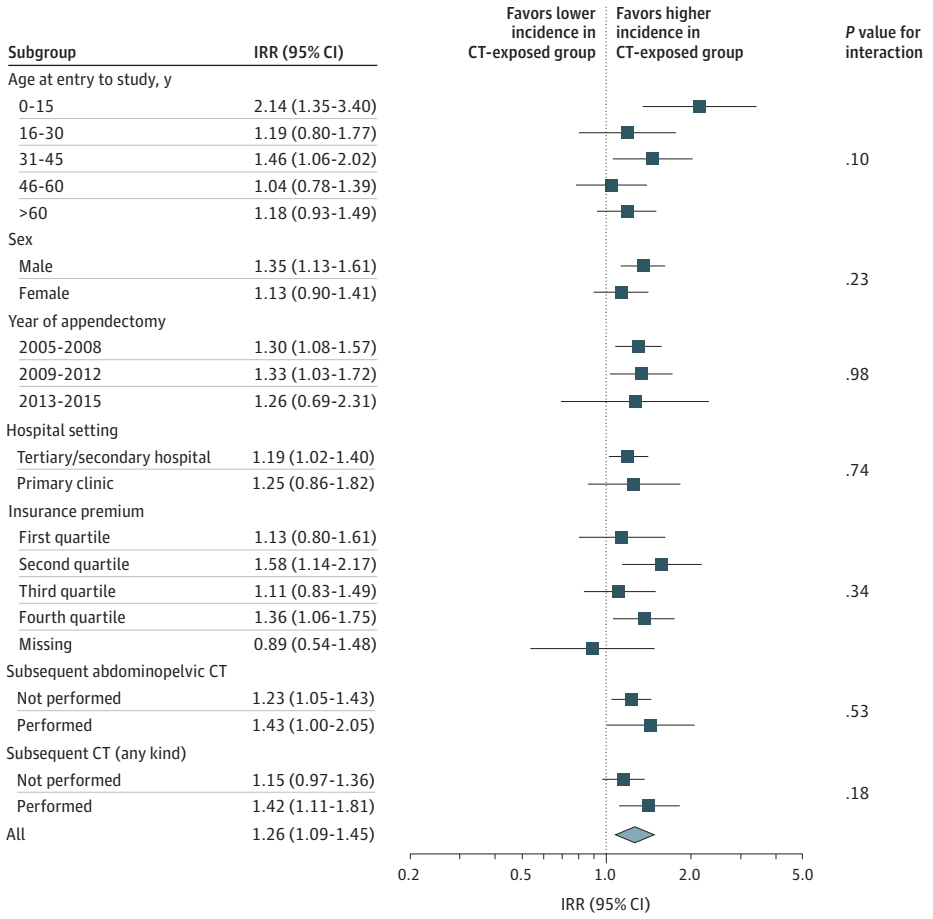
There was no obvious tendency for the incidence rate to increase with the number of any CT examinations (P = .66 for linear trend). The IRRs for hematologic malignant neoplasms were 1.09 (95% CI, 0.93-1.27) for patients with 1 CT examination and 1.16 (95% CI, 0.96-1.40) in patients with at least 2 CT examinations (eTable 7 in the Supplement).

Discussion

In this Korean nationwide study, we found that hematologic malignant neoplasms occurred more frequently in the CT-exposed group than in the CT-unexposed group (IRR, 1.26 [95% CI, 1.09-1.45]). The incidence of hematologic malignant neoplasms tended to increase with the number of abdominopelvic CT examinations. The carcinogenic risk from abdominopelvic CT radiation was most pronounced in patients aged 0 to 15 years (IRR, 2.14 [95% CI, 1.35-3.40]). This finding is in line with the knowledge that pediatric patients are more radiosensitive than adult patients. Most of the excess hematologic malignant neoplasms were leukemia, particularly myeloid leukemia. Our study corroborates the results from the Japanese Life Span study[32] in which the radiation-associated excess risks were most evident in leukemia, and especially in myeloid leukemia.

It has been highly debatable whether CT radiation can truly induce cancers.[1,2] The results of previous large epidemiological studies[4-8] have been inconsistent regarding this issue. Although studies from the United Kingdom,[4] Australia,[5] and

Figure 3. Forest Plots of Subgroup Analyses



Data are given as incidence rate ratios (IRRs) of all hematologic malignant neoplasms across subgroups. Diamond indicates IRR of all study patients (center) and 95% CI (ends).

South Korea[8] reported significant association between CT radiation and hematologic malignant neoplasms, studies from Taiwan,[6] the Netherlands,[7] France,[10] and Germany[11] found no such association. Our study is distinguished from the previous studies in that we specified the reasons for the CT scan (ie, preoperative diagnosis of appendicitis and postoperative evaluation of complication) to disentangle radiation effects from the reasons why the CT examinations were performed. Because previous epidemiological studies[4-8] did not specify the reasons for the CT scan that were counted as exposure, a substantial portion of those CT examinations may have been performed to detect or manage cancers, rather than causing these cancers.[1-3] To overcome the reverse causation bias and confounding by indication, researchers have adopted various lag periods[4,5,7,8] or retrospectively reviewed medical records to identify the underlying conditions or the reasons for CT scans.[10-12] Nonetheless, concerns for biases have remained in the previous studies.[1-3]

In contrast to the studies that showed an association of CT radiation with solid cancer development,[4-8] such an association in our study was neither obvious nor statistically significant. Previous studies showed an excessive risk of solid cancers even within the first 5 years after CT exposure,[5,7] whereas the Japanese Life Span study[33] reported that the risk appeared around 10 years after the atomic bomb exposure. Statistical association between CT radiation and carcinogenesis may be more prone to reverse causation bias for solid cancers than for hematologic malignant neoplasms. Computed tomographic examinations are not routinely performed for the diagnosis of leukemia, whereas CT is among key diagnostic tests for the diagnosis of solid cancer. In addition, acute leukemia generally develops rapidly, whereas solid cancers grow more slowly, producing symptoms that prompt CT examinations long before clinical diagnosis.

From our results, we are not claiming that use of periappendectomy CT should be discouraged in all patients. Historically, the increase in the use of CT coincided with the reduction of negative appendectomy rates.[34,35] Doses of CT radiation are now likely to be lower than those used in this cohort, owing to advances in the technology and the efforts of physicians.[36,37] Thus, the association between the incidence of hematologic malignant neoplasms and CT radiation may be smaller with modern CT machines. Deferring CT examinations that are medically justifiable would put patients at risk of harm greater than potential carcinogenesis.[38] Nevertheless, it should be noted that no formal research has examined whether overall benefit of CT examinations truly outweighs the radiation-associated carcinogenic risk. At least in chil-

dren, the importance of judicious use of CT cannot be overstated, as suggested by the high IRR for hematologic malignant neoplasms in children younger than 16 years.

Limitations

Our study had several limitations. First, the follow-up duration was limited. Longer follow-up may have shown more pronounced carcinogenic risk of CT radiation. Second, the comparability between the CT-exposed and CT-unexposed groups may have been limited because we could not adjust for many potential confounders such as exposure to carcinogens in food or environment, occupational radiation, smoking, and alcohol. Unfortunately, such data were not available in the database or were missing not at random in more than half of the patients. We also did not adjust for medical radiation exposure other than CT. Other radiologic examinations usually have considerably lower radiation doses compared with CT, but there nevertheless might have been added risks that we could not account for. Third, our catchment area was limited to South Korea, where the population is ethnically homogeneous, and it is uncertain whether our results can be generalized to other populations. Finally, individual dosimetry data were not available. Our estimation of the mean red bone marrow dose based on the national survey data is likely to be limited owing to considerable variation in CT radiation doses across institutions and individual patients.[25,39]

Conclusions

In our nationwide study where reverse causation bias was controlled by defining the reasons for the CT scan, even one-time radiation exposure to abdominopelvic CT was associated with a higher incidence of hematologic malignant neoplasms. Efforts should be continued for judicious use of CT examinations, particularly in children.

ARTICLE INFORMATION

Accepted for Publication: November 7, 2020.

Published Online: January 20, 2021. doi:10.1001/jamasurg.2020.6357

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Administrative, technical, or material support: Park.
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Conflict of Interest Disclosures: Dr Kyung Hee Lee reported receiving grants from the National Research Foundation of Korea funded by the Korea government outside the submitted work. Dr Park reported receiving grants from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education and Seoul National University Bundang Hospital Research Fund. No other disclosures were reported.

Funding/Support: This research was supported by grant NRF-2018R1D1A1B07050976 for the Basic Science Research Program through the National Research Foundation of Korea from the Ministry of Education and grant 14-2018-008 from the Seoul National University Bundang Hospital Research Fund.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Choonsik Lee, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, provided advice in improving the manuscript, for which he was not compensated.

REFERENCES

1. Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. Risks from CT scans—what do recent studies tell us? *J Radiol Prot*. 2014;34(1):E1-E5. doi:10.1088/0952-4746/34/1/E1

2. Boice JD Jr. Radiation epidemiology and recent paediatric computed tomography studies. *Ann ICRP*. 2015;44(1, suppl):236-248. doi:10.1177/0146645315575877

3. Harvey HB, Brink JA, Frush DP. Informed consent for radiation risk from CT is unjustified based on the current scientific evidence. *Radiology*. 2015;275(2):321-325. doi:10.1148/radiol.2015142859

4. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380(9840):499-505. doi:10.1016/S0140-6736(12)60815-0

5. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ*. 2013;346:f2360. doi:10.1136/bmj.f2360

6. Huang WY, Muo CH, Lin CY, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. *Br J Cancer*. 2014;110(9):2354-2360. doi:10.1038/bjc.2014.103

7. Meulepas JM, Ronckers CM, Smets AMJB, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. *J Natl Cancer Inst*. 2019;111(3):256-263. doi:10.1093/jnci/djy104

8. Hong JY, Han K, Jung JH, Kim JS. Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea. *JAMA Netw Open*. 2019;2(9):e1910584. doi:10.1001/jamanetworkopen.2019.10584

9. Shore RE, Beck HL, Boice JD, et al. Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection. *J Radiol Prot*. 2018;38(3):1217-1233. doi:10.1088/1361-6498/aad348

10. Journy N, Rehel JL, Ducou Le Pointe H, et al. Are the studies on cancer risk from CT scans biased by indication? elements of answer from a large-scale cohort study in France. *Br J Cancer*. 2015;112(1):185-193. doi:10.1038/bjc.2014.526

11. Krille L, Dreger S, Schindel R, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. *Radiat Environ Biophys*. 2015;54(1):1-12. doi:10.1007/s00411-014-0580-3

12. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. *Br J Cancer*. 2016;114(4):388-394. doi:10.1038/bjc.2015.415

13. Coursey CA, Nelson RC, Patel MB, et al. Making the diagnosis of acute appendicitis: do more preoperative CT scans mean fewer negative appendectomies? a 10-year study. *Radiology*. 2010; 254(2):460-468. doi:10.1148/radiol.09082298

14. Cuschieri J, Florence M, Flum DR, et al; SCOAP Collaborative. Negative appendectomy and imaging accuracy in the Washington State surgical care and outcomes assessment program. *Ann Surg*. 2008; 248(4):557-563.

15. Park JH; LOCAT Group. Diagnostic imaging utilization in cases of acute appendicitis: multi-center experience. *J Korean Med Sci*. 2014;29 (9):1308-1316. doi:10.3346/jkms.2014.29.9.1308

16. Ferris M, Quan S, Kaplan BS, et al. The global incidence of appendicitis: a systematic review of population-based studies. *Ann Surg*. 2017;266(2): 237-241. doi:10.1097/SLA.0000000000002188

17. Little MP, Wakeford R, Borrego D, et al. Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies. *Lancet Haematol*. 2018;5(8):e346-e358. doi:10.1016/S2352-3026(18) 30092-9

18. Basic anatomical and physiological data for use in radiological protection: reference values: ICRP publication 89. *Ann ICRP*. 2002;32(3-4):1-277. doi:10.1016/S0146-6453(03)00002-2

19. ClinicalTrials.gov. CT carcinogenic risk in patients with appendicitis. NCT03776435. Accessed December 5, 2020. https://clinicaltrials.gov/ct2/show/NCT03776435

20. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

21. Benchimol EI, Smeeth L, Guttmann A, et al; RECORD Working Committee. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885

22. Medical Radiation Bulletin Board. Guidelines for the reference level of diagnosis in computed tomography: diagnostic reference level in Korea—national survey in 2008. Updated March 8, 2008. Accessed April 1, 2020. http://www.cdc.go.kr/board.es?mid=a20305050000&bid=0003&act=view&list_no=127231

23. Hwang JY, Do KH, Yang DH, et al. A survey of pediatric CT protocols and radiation doses in South Korean hospitals to optimize the radiation dose for pediatric CT scanning. *Medicine (Baltimore)*. 2015; 94(50):e2146. doi:10.1097/MD.0000000000002146

24. Kim KP, Berrington de González A, Pearce MS, et al. Development of a database of organ doses for paediatric and young adult CT scans in the United Kingdom. *Radiat Prot Dosimetry*. 2012;150(4): 415-426. doi:10.1093/rpd/ncr429

25. Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr*. 2013;167(8):700-707. doi:10.1001/jamapediatrics.2013.311

26. Berrington de Gonzalez A, Journy N, Lee C, et al. No association between radiation dose from pediatric CT scans and risk of subsequent Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*. 2017;26(5):804-806. doi:10.1158/1055-9965.EPI-16-1011

27. United Nations Scientific Committee on the Effects of Atomic Radiation. Effects of ionizing radiation: UNSCEAR 2006 report to the general assembly, with scientific annexes. Updated June 26, 2016. Accessed December 5, 2020. https://www.unscear.org/unscear/en/publications/2006_1.html

28. Hwangbo Y, Kang D, Kang M, et al. Incidence of diabetes after cancer development: a Korean national cohort study. *JAMA Oncol*. 2018;4(8): 1099-1105. doi:10.1001/jamaoncol.2018.1684

29. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. *Gut*. 2018;67(5):945-952. doi:10.1136/gutjnl-2017-314904

30. Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. *Asian Pac J Cancer Prev*. 2012;13(12):6163-6168. doi:10.7314/APJCP.2012.13.12.6163

31. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30. doi:10.3322/caac.21590

32. Hsu WL, Preston DL, Soda M, et al. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. *Radiat Res*. 2013;179(3):361-382. doi:10.1667/RR2892.1

33. Ozasa K, Grant EJ, Kodama K. Japanese legacy cohorts: the life span study atomic bomb survivor cohort and survivors' offspring. *J Epidemiol*. 2018; 28(4):162-169. doi:10.2188/jea.JE20170321

34. Drake FT, Florence MG, Johnson MG, et al; SCOAP Collaborative. Progress in the diagnosis of appendicitis: a report from Washington State's surgical care and outcomes assessment program. *Ann Surg*. 2012;256(4):586-594. doi:10.1097/SLA.0b013e31826a9602

35. Raman SS, Osuagwu FC, Kadell B, Cryer H, Sayre J, Lu DS. Effect of CT on false positive diagnosis of appendicitis and perforation. *N Engl J Med*. 2008;358(9):972-973. doi:10.1056/NEJMc0707000

36. LOCAT Group. Low-dose CT for the diagnosis of appendicitis in adolescents and young adults (LOCAT): a pragmatic, multicentre, randomised controlled non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2017;2(11):793-804. doi:10.1016/S2468-1253(17)30247-9

37. Kim K, Kim YH, Kim SY, et al. Low-dose abdominal CT for evaluating suspected appendicitis. *N Engl J Med*. 2012;366(17):1596-1605. doi:10.1056/NEJMoa1110734

38. Hendee WR, O'Connor MK. Radiation risks of medical imaging: separating fact from fantasy. *Radiology*. 2012;264(2):312-321. doi:10.1148/radiol.12112678

39. Ekpo EU, Adejoh T, Akwo JD, et al. Diagnostic reference levels for common computed tomography (CT) examinations: results from the first Nigerian nationwide dose survey. *J Radiol Prot*. 2018;38(2):525-535. doi:10.1088/1361-6498/aaaaf8

Invited Commentary

Optimizing the Gold Standard—Low-Dose Computed Tomography Modalities as a Part of Clinical Practice in Acute Appendicitis Imaging

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Suspicion of appendicitis is globally one of the most common reasons for emergency surgical visits, with appendectomy as the standard treatment for all appendicitis cases for more than a century, even though both epidemiological and clinical data have shown uncomplicated and complicated acute appendicitis being distinct entities instead of consecutive events. Antibiotics are shown to be a safe and efficient alternative to appendectomy for patients with imaging-confirmed, uncomplicated appendicitis, both in adults[1] and children,[2] setting new standards for preinterventional appendicitis diagnostics and shifting the emphasis from solely assessing the presence of appendicitis toward distinguishing between uncomplicated and complicated appendicitis with high accuracy. This requires imaging, with computed tomography (CT) being the gold standard in adults. However, the main disadvantage of CT is exposure to radiation. The high appendicitis incidence in adolescents and young adults more sensitive to the late effects of radiation emphasizes the need to reduce the CT dose.

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In this issue of *JAMA Surgery*, Lee et al[3] report a higher incidence of hematologic malignant conditions associated with