Results of low-dose computed tomography as a regular health examination among Chinese hospital employees

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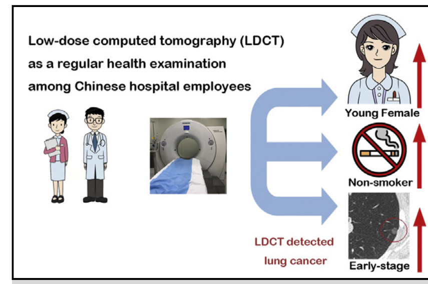
ABSTRACT

Objective: Lung cancer is traditionally more prevalent in the elderly patients, men, and smokers. However, as low-dose computed tomography (LDCT) is increasingly popular, we hypothesized the disease spectrum might change.

Methods: LDCT was performed as a part of regular health examinations in 8392 of 15,686 employees from 6 hospitals in different regions of China in 2012 to 2018. Clinicopathologic characteristics, including age, sex, smoking status, radiologic features, tumor histology, and pathologic stage, were retrospectively analyzed.

Results: LDCT incidentally detected lung cancer (pathologically confirmed) in a total of 179 (2.1%) hospital employees. The lung cancer detection rate was significantly greater in female than male (2.5% vs 1.3%, $P = .001$) patients. There was also a greater detection rate among nonsmokers than smokers, although statistical significance was not reached (2.2% vs 1.4%, $P = .092$). The lung cancer detection rate was 1.0% in the "age $\leq$40 years" group, 2.6% in the "40 $<$ age $\leq$55 years" group, and 2.9% in the "age $>$55 years" group ($P < .001$). Among the hospital employees with lung cancer, 171 (95.5%) presented as ground-glass opacity, 177 (98.9%) were lung adenocarcinoma, 170 (95.0%) were early stage 0/IA, and 177 (98.9%) received curative surgical resection as the initial treatment. After a median follow-up of 38 months, no disease recurrence or death was observed among these patients.

Conclusions: LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage, with extremely good prognosis. (J Thorac Cardiovasc Surg 2020;160:824-31)



LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees.

CENTRAL MESSAGE

LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage with an extremely good prognosis.

PERSPECTIVE

Lung cancer is traditionally more prevalent in the elderly patients, men, and smokers. We found LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage with extremely good prognosis. There are challenges and opportunities for better understanding and management of this disease.

See Commentaries on pages 832, 833, 835, and 836.

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Abbreviations and Acronyms

AAH = atypical adenomatous hyperplasia
AIS = adenocarcinoma in situ
FUSCC = Fudan University Shanghai Cancer Center
GGO = ground-glass opacity
LDCT = low-dose computed tomography
MIA = minimally invasive adenocarcinoma
NLST = National Lung Cancer Screening Trial

Supplemental material is available online.

Video clip is available online.

Lung cancer remains a major cause of cancer-related death worldwide.[1] Classically, lung cancer is more prevalent in the elderly patients, men, and smokers and is usually diagnosed at a late stage. The National Lung Cancer Screening Trial (NLST) demonstrated a relative reduction in mortality from lung cancer with low-dose computed tomography (LDCT) screening of 20.0%.[2] According to that study, eligible high-risk participants for LDCT screening were 55 to 74 years of age and had at least 30 pack-year histories of smoking.[2] The Early Lung Cancer Action Project found that annual LDCT screening can detect curable lung cancer.[3]

LDCT, as an alternative to chest radiography, is becoming increasingly popular in some regions of China, especially after the release of the NLST trial data.[2] In China, LDCT is cheap (about 30 US dollars) and can usually be performed on the same day of appointment. It is popular not only in the "high-risk" population defined by the NLST trial, but also in the "low-risk" population. Many companies (including hospitals) offer LDCT to their employees as a part of the regular annual health examination, regardless of age and smoking history. In our daily clinical work, we observed that LDCT incidentally detected lung cancer in a significant proportion of the "low-risk" population. This study focused on the incidental lung cancer detected by LDCT as a regular annual health examination in hospital employees to elaborate this phenomenon.

METHODS

Study Design and Patients

LDCT was performed as a part of regular annual health examination among hospital employees (including retired) from 6 hospitals in different regions of China between 2012 and 2018: Fudan University Shanghai Cancer Center (FUSCC), Shanghai Xinhua Hospital, Shanghai Huadong Hospital, Liaocheng Second People's Hospital in Shandong, Jiang du People's Hospital in Jiangsu, and People's Hospital of Jieyang Industrial Transfer Park in Guangdong. Health examination policies varied among different hospitals. However, in general, LDCT was offered to employees who volunteered to take the test in these hospitals. Surgical resection could be considered for persistent LDCT-detected lung ground-glass opacity (GGO) nodules $\geq$6 mm in size. LDCT-detected lung solid nodules were managed according to the National Comprehensive Cancer Network guidelines.[4] Employees with pathologically confirmed lung cancer in each hospital were recorded. In fact, some employees with suspicious malignant nodules were still in follow-up. Clinicopathologic characteristics, including age, sex, smoking status, tumor histology, disease stage, and initial treatment, were retrospectively analyzed. Nonsmokers were defined as patients who had never smoked cigarettes in their lifetime. This study was approved by the institutional review board of each participating center.

Statistical Analysis

We used the Pearson χ^2 test to compare the lung cancer detection rate. Statistical analysis was performed in R (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of Hospital Employees and LDCT Participation Rates

There were a total of 15,686 employees in the 6 hospitals. The proportion of female employees was 70.7% (61.1%-75.1%). The percentages of patients $\leq$40 years, 41 to 55 years, and >55 years were 57.1% (47.2%-73.5%), 20.1% (14.3%-25.5%), and 22.9% (4.3%-31.3%), respectively. Nonsmokers accounted for 91.4% (3.8%-26.3%). The overall LDCT participation rate was 53.5% (30.4%-100.0%). In total, LDCT incidentally detected lung cancer (pathologically confirmed) in 179 (2.1%) hospital employees from 2012 to 2018 in the 6 hospitals (Table 1). Fourteen employees underwent surgery for LDCT findings but did not have cancer: 4 had atypical adenomatous hyperplasia (AAH) and 10 had benign disease. Twelve employees had GGO lesions that disappeared during follow-up and did not receive surgery, and 3 employees with centrally located small GGO lesions were still in follow-up.

Proportion of Hospital Employees With Lung Cancer According to Sex, Age, and Smoking History

Among employees with lung cancer, 147 (82.1%) were female and 32 (17.9%) were male; 167 (93.3%) were nonsmokers. The lung cancer detection rate was significantly greater in female than male (2.5% vs 1.3%, $P = .001$) patients. There was also a greater detection rate among nonsmokers than smokers, although statistical significance was not reached (2.2% vs 1.4%, $P = .092$). However, the greater detection rate among nonsmokers was probably due to the high proportion of female participants since lung cancer detection rate was comparable among male nonsmokers and male smokers (1.2% vs 1.4%, $P = .775$). The lung

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TABLE 1. Characteristics of hospital employees and LDCT participation rates in each hospital

Hospital	Total no. of employees	Female	Nonsmokers	Age, y (≤40/41-55/>55)	No. of employees receiving LDCT
1	2740	1932 (71%)	2635 (96%)	1731/391/618 (63%/14%/23%)	2291 (84%)
2	1519	1039 (68%)	1162 (76%)	845/387/278 (56%/25%/18%)	675 (44%)
3	2859	1909 (67%)	2590 (91%)	2045/506/308 (72%/18%/11%)	868 (30%)
4	4779	3591 (75%)	4526 (95%)	2424/1050/1305 (51%/22%/27%)	1551 (32%)
5	3344	2346 (70%)	3092 (92%)	1580/716/1048 (47%/21%/31%)	2562 (77%)
6	445	272 (61%)	328 (74%)	327/99/19 (73%/22%/4%)	445 (100%)
Total	15,686	11,089 (71%)	14,333 (91%)	8952/3149/3585 (57%/20%/23%)	8392 (53%)

Hospital 1: Fudan University Shanghai Cancer Center; Hospital 2: Jiang du People's Hospital; Hospital 3: Liaocheng Second People's Hospital; Hospital 4: Shanghai Xinhua Hospital; Hospital 5: Shanghai Huadong Hospital; Hospital 6: People's Hospital of Jieyang Industrial Transfer Park. *LDCT*, Low-dose computed tomography.

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cancer detection rate was 1.0% in the "age ≤40 years" group, 2.6% in the "40 < age ≤ 55 years" group, and 2.9% in the "age >55 years" group (*P* < .001) (Table 2).

Radiologic Features, Tumor Histology, Disease Stage, and Initial Treatment

Among the 179 hospital employees with lung cancer, there were 177 (98.9%) lung adenocarcinoma (46 adenocarcinoma in situ [AIS], 67 minimally invasive adenocarcinoma [MIA], and 64 invasive adenocarcinoma), 1 (0.6%) lung squamous cell carcinoma, and 1 (0.6%) carcinoid. The early stage 0/IA patients accounted for 95.0%. Only 1 patient had stage IV lung cancer. The majority of these tumors presented as GGO on CT scans.

TABLE 2. The proportion of hospital employees with lung cancer according to sex, age, and smoking history

Characteristics	No. of employees receiving LDCT	No. of lung cancers	Lung cancer detection rate, %	*P* value
Sex				.001
Female	5908	147	2	
Male	2484	32	1	
Smoking history				.092
Nonsmokers	7509	167	2	
Ever-smokers	883	12	1	
Male employees				.775
Nonsmokers	1612	20	1	
Ever-smokers	872	12	1	
Age, y				<.001
≤40	3067	31	1	
41-55	2530	66	3	
>55	2795	82	3	

LDCT, Low-dose computed tomography.

The patient with stage IV lung cancer received chemotherapy followed by radiotherapy. Another patient with clinical stage IA lung adenocarcinoma received stereotactic body radiotherapy because of elder age (88 years old). The rest 177 patients received curative surgical resection as the initial treatment (Table 3).

Survival Outcomes

Until February 2019, none of the hospital employees with LDCT-detected lung cancer died. The median follow-up time was 38 (range: 3-80) months. Disease recurrence was not observed in any of the employees who received surgery as the initial treatment.

DISCUSSION

LDCT was performed in China after 2000 and is becoming increasingly popular, especially after the publication of the NLST trial results.[2] Our study of hospital employees showed LDCT incidentally detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage with extremely good prognosis. Actually, this phenomenon is not limited to hospital employees. In our community-based LDCT screening program conducted in Shanghai from 2013 to 2014, a high lung cancer detection rate was found among women and nonsmokers.[5] Additional data supporting this phenomenon were shown in the Supplementary Methods and Results (Table E1 and Figures E1-E3). We focused on hospital employees because data from hospitals are generally more accurate. The strong association between smoking and death from lung cancer was well demonstrated by a study on male British doctors.[6] Our findings are in contradictory

TABLE 3. Radiologic features, tumor histology, disease stage, and initial treatment of the 179 hospital employees with lung cancer

Characteristics	n (%)
Radiologic features	
Ground-glass opacity	171 (96)
Solid	8 (4)
Tumor histology	
Adenocarcinoma	177 (99)
Adenocarcinoma in situ	46 (26)
Minimally invasive adenocarcinoma	67 (37)
Invasive adenocarcinoma	64 (36)
Squamous cell carcinoma	1 (0.6)
Carcinoid	1 (0.6)
Stage	
0	46 (26)
IA	124 (69)
IB	4 (2)
IIA	1 (0.6)
IIB	1 (0.6)
IIIA	2 (1)
IV	1 (0.6)
Initial treatment	
Surgery	177 (99)
Chemoradiation	1 (0.6)
Radiotherapy	1 (0.6)
Total	179 (100)

to classical notions of lung cancer and require paradigm shift in our thinking.

Young, nonsmoking women are not traditionally a "high-risk" population of lung cancer as defined by the NLST trial. It is still unclear whether the increasing trend of lung cancer in young female nonsmokers can be attributed to early detection by LDCT or a real rising incidence. Moreover, whether there is a survival benefit of screening young female nonsmokers remains unknown, and future randomized screening trials should consider including these populations. However, in Shanghai and Korea, lung cancer mortality rate in women was decreasing significantly despite the increasing incidence.[7] In FUSCC, the 5-year recurrence-free survival rate and 5-year overall survival rate of 583 patients with lung cancer presenting as $\leq$2 cm GGO (February 2010 to December 2014) reached 98.0% and 99.1%, respectively. The 5-year overall survival rate for 1187 patients with stage IA lung cancer (April 2008 to February 2015) reached 94.0%. However, long-term follow-up is still needed to evaluate the prognosis of these patients. Recently, Jemal and colleagues[8] reported a greater lung cancer incidence in young women than young men in the United States. Similarly, Olajide and colleagues[9] observed that lung cancer incidence in England increased in women and decreased in men between 2002 and 2011. Will there be more young, female, nonsmoking patients with lung cancer in Western countries if LDCT is performed in these populations?

Another important question is why do young, female, nonsmokers have lung cancers? Lung cancer incidence was declining after tobacco smoking was identified as the major risk factor and tobacco-control programs were undertaken.[1,10,11] Therefore, our findings should raise global awareness to the identification of risk factors associated with young, female, nonsmoking patients with lung cancers. Although there are environmental risk factors other than smoking, such as exposure to secondhand smoke, contact with kitchen fumes, hormones, radon, asbestos or air pollution, a large proportion of nonsmoking patients with lung cancer don't have definite association with established environmental risk factors.[12] At least, we don't have evidence supporting exposure to environmental risk factors in employees of the 6 hospitals in China. Working in a hospital is not likely to be a risk factor because, for example, lung cancer was detected in 2 young (21 and 22 years old, respectively) nurses of FUSCC who had just graduated from nursing school. Genetic predisposition to lung cancer remains largely unknown. In the future, epidemiologists, doctors, geneticists, and basic researchers should work together to clarify the etiology.

Most of these LDCT-detected lung cancers present as small GGOs on computed tomography. The first issue is about diagnosis and follow-up for small GGO lesions. In FUSCC, 92.6% of patients with resected GGO nodules turned out to have lung cancers or AAH. However, there is no perfect method to distinguish the benign and malignant GGO with 100% accuracy. In our experience, a period of follow-up (4-6 months) may be helpful to make differential diagnosis. During follow-up, benign GGOs may disappear (Figure 1, *A-D*), whereas the majority of those unchanged (Figure 1, *E-H*) or enlarged (Figure 1, *I-O*) GGOs turn out to be malignant.

The guideline-recommended surgery for early-stage lung cancer is still lobectomy plus mediastinal lymph node dissection.[13] For some early-stage lung cancer, lobectomy is definitely an "overtreatment." In addition, current recommendations of preoperative diagnostic tests and postoperative follow-up are not tailored individually for patients with LDCT-detected early-stage lung cancer.[13] Therefore, we have done a lot of work to improve the clinical practice including preoperative workups, range of surgical resection, and postoperative follow-up.

Our first contribution is to simplify preoperative workups. Our data demonstrated that bronchoscopy was unrevealing for patients with $\leq$3 cm GGO lesions.[14] Bone metastasis was not found in patients with cT1N0 pure GGO lesions.[15] None of the patients with cT1N0 GGO lesions had brain metastasis. Prospective trials for omitting bronchoscopy (NCT03591445), magnetic resonance

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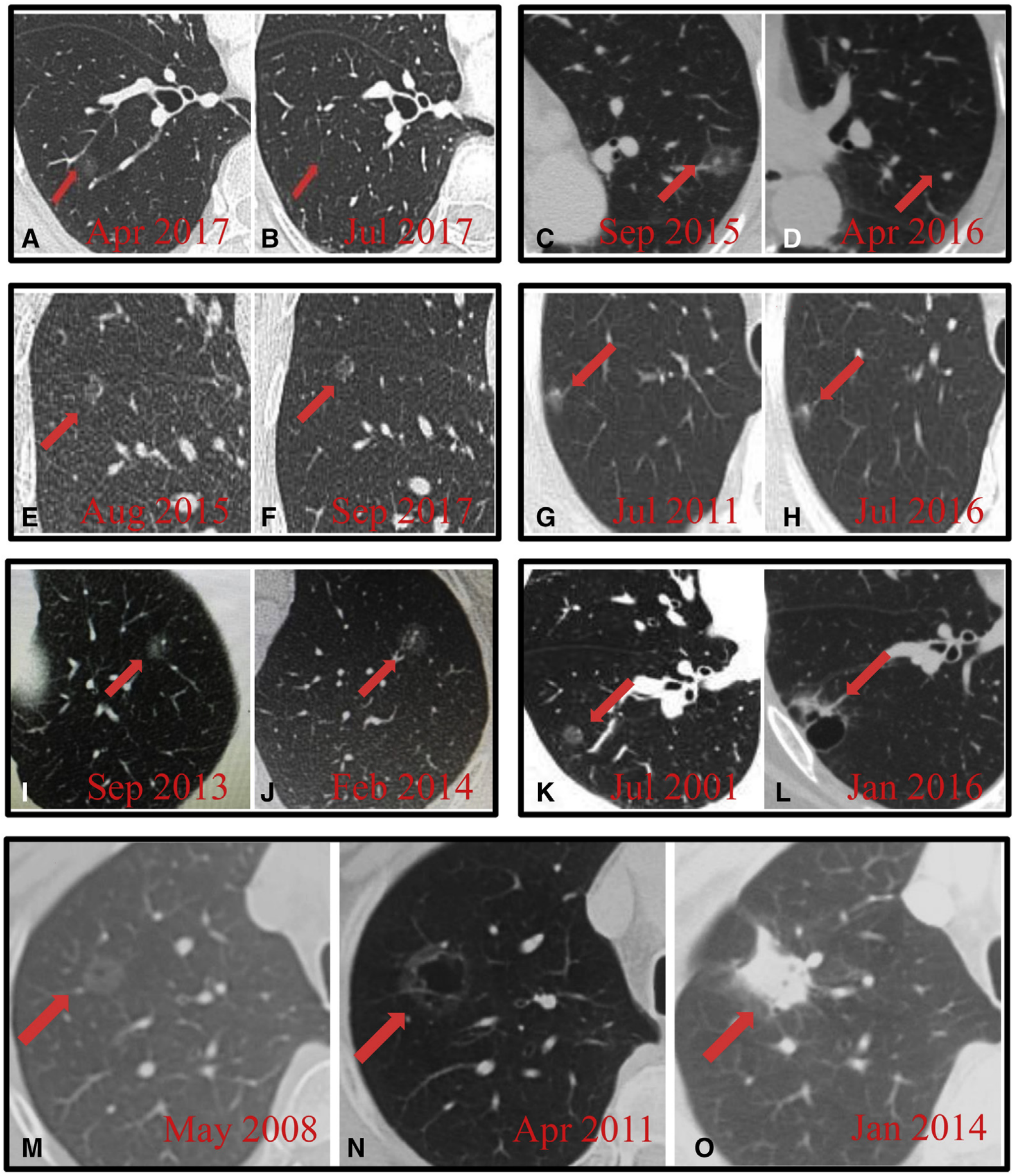


FIGURE 1. Examples of GGO nodules that disappeared (A-D), remained unchanged (E-H), or enlarged (I-O). A-D, Examples of GGO nodules that disappeared after 3 months (A-B) and 8 months (C-D) of follow-up. E-H, Examples of GGO nodules that remained unchanged after 2 years (E-F) and 5 years (G-H) of follow-up. The final pathology was minimally invasive adenocarcinoma for both GGO nodules. I-J, A GGO nodule that enlarged from 0.7 cm (I) to 1.1 cm (J) after 5 months of follow-up. The tumor VDT was 77 days. The final pathology was acinar predominant adenocarcinoma, pT1aN0M0. K-L, A 65-year-old woman with a nodule that enlarged significantly from July 2001 (K) to January 2016 (L). The final pathology was acinar predominant adenocarcinoma, pT1bN0M0. The VDT was 1159 days. M-O, A GGO nodule that became larger and more solid gradually after 6 years of follow-up.

imaging of the brain, or bone scan (NCT03689439) in selected lung cancer patients are ongoing in FUSCC.

Most importantly, surgical resection including lung parenchymal resection and lymph node resection for small-sized, early-stage lung cancer is individualized in our center. Our previous study demonstrated that intraoperative frozen section can precisely distinguish invasive adenocarcinoma from MIA/AIS/AAH (concordance rate: 95.9%) and effectively guide resection strategy for small-sized (≤3 cm) peripheral lung adenocarcinoma. We performed lobectomy for invasive adenocarcinoma and sublobectomy for MIA/AIS/AAH (Video 1). The 5-year recurrence-free survival rate was 100% for patients with MIA or AIS.[16] Our finding was "an important step toward personalization of surgical care for early-stage lung cancer."[17] Our previous study also found no lymph node metastasis in small (≤2 cm) peripheral AIS, MIA, lepidic predominant adenocarcinoma, invasive mucinous

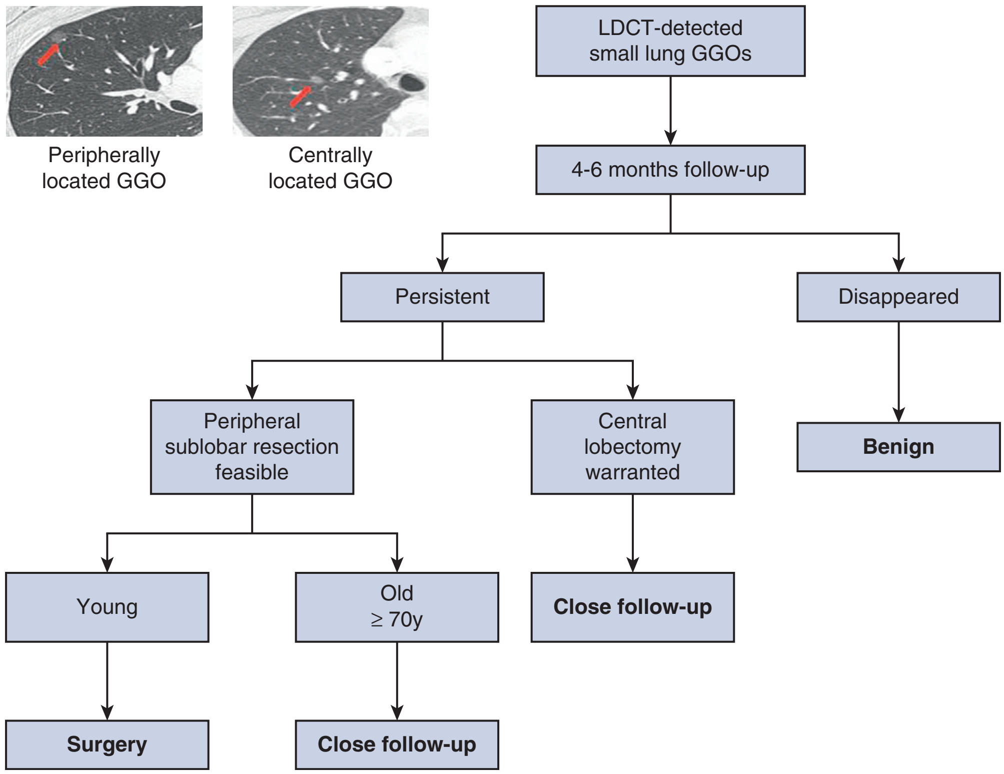


FIGURE 2. Approaches to managing LDCT-detected small lung GGO nodules in Fudan University Shanghai Cancer Center. After 4 to 6 months of follow-up, benign GGO nodules may disappear. For patients with persistent small GGOs, whether active surgical intervention is necessary should take into account the location of the nodule and age at diagnosis. For young patients with peripheral GGO lesions that can be managed by limited resection, early intervention is advocated, whereas for relatively centrally located small GGOs that require lobectomy or elderly (≥70 years) patients who have a short life expectancy, close follow-up is suggested. *GGO*, Ground-glass opacity; *LDCT*, low-dose computed tomography.

adenocarcinoma, or squamous cell carcinoma.[18] For these patients, systematic lymph node dissection might be avoided. A prospective trial of selective mediastinal lymph node dissection according to tumor histology and location is ongoing in FUSCC (NCT03216551). In addition, in our opinion, the size/number of surgical incisions, the extent of resection, and the systemic damage by surgery should be taken into consideration to minimize surgical trauma.[19]

After sublobar resection, patients with early-stage lung cancer can return to normal social lives within 1 week after surgery, just like healthy people. In this study, hospital employees after surgery all returned to work and life as normal. Current guidelines recommend that patients with stage I-II should be followed-up every 6 months for 2 to 3 years.[13] However, our data showed that patients with resected early-stage lung cancers, especially small GGO lesions, have good prognosis, suggesting a less-intensive postoperative follow-up strategy may be more appropriate.

Some may deem the detection of small GGO nodules by LDCT as "overdiagnosis." It was estimated that 18.5% of lung cancer detected by LDCT screening were an overdiagnosis because of indolent behavior.[20] However, studies of natural histories of GGOs found that about 20% of pure GGOs and 40% of part-solid GGOs grew in size or became more solid after a mean or median follow-up time of 2.4 to 4.9 years.[21] In our clinical experience, we have observed untreated small-sized lung GGO nodules became larger and more solid and therefore required more extensive treatment. For example, a 50-year-old woman with a small lung nodule could have been managed by wedge resection (Figure 1, *K*). However, the nodule became larger and more solid after 15 years, and the woman had to receive lobectomy to treat this nodule at the age of 65 (Figure 1, *L*). The final pathology was acinar predominant adenocarcinoma (pT1bN0M0). For this patient, wedge resection at 50 years old is better than lobectomy at 65 years old. In contrast, however, some GGO lesions progress quickly (Figure 1, *I* and *J*), whereas others may not change in a long period of time (Figure 1, *G* and *H*), although they eventually turn out to be malignant. The exact time to intervene is still unknown and is largely dependent on the aggressiveness of the nodule.

How to distinguish the aggressive tumors from the indolent tumors? Our previous study showed a part-solid component, large consolidation size, and large tumor size were associated with pathologic invasive adenocarcinoma

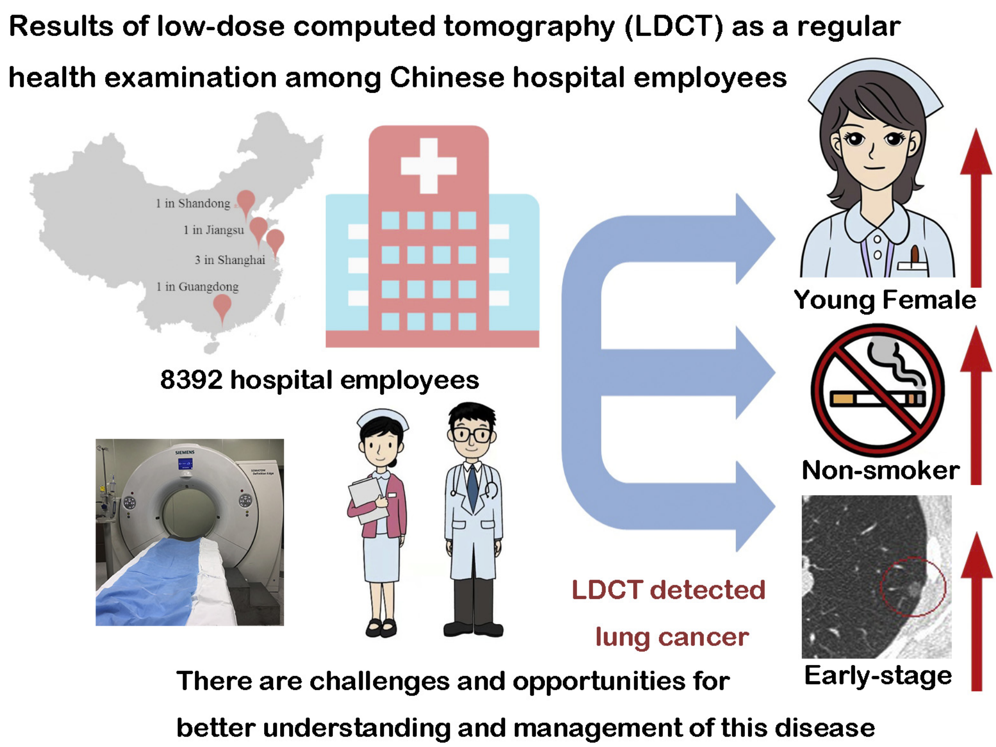


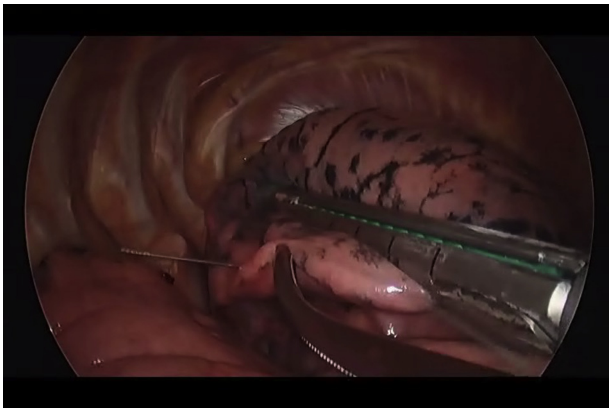
FIGURE 3. Methods, results, and implications of this study. We analyzed the results of LDCT as a regular health examination in 8392 of 15,686 employees from 6 hospitals in different regions of China. We found LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage, with extremely good prognosis. There are challenges and opportunities for better understanding and management of this disease. *LDCT*, Low-dose computed tomography.

among GGO lesions.[22] We also found that there was no recurrence for patients with pure GGOs after surgery, whereas a proportion of patients with part-solid GGOs had disease recurrence after surgical resection.[23] We are currently performing whole-exome sequencing and RNA sequencing analysis of early-stage lung cancers including AIS, MIA, and invasive adenocarcinoma with or without postoperative recurrence and aim to find key molecular alterations underlying disease progression.

After a period of follow-up, for patients with persistent small GGOs, we believe that whether active surgical intervention is necessary should take into account the location of the nodule and age at diagnosis. For young patients with peripheral GGO lesions that can be managed by limited resection, we advocate early intervention, whereas for relatively centrally located small GGOs that require lobectomy or elderly ($\geq$70 years) patients who have a short life expectancy, we suggest close follow-up. Approaches to manage LDCT-detected small lung GGO lesions were described in Figure 2. These approaches are applied to all patients (not limited to hospital employees).

Limitations

Our study has several limitations. First, this study is not a screening trial, and many questions remain unsolved. For example, whether there is a survival benefit for LDCT screening in the "low-risk" population, the optimal interval for screening, the cost–benefit ratio, the efficacy of surgery,



VIDEO 1. A representative video of wedge resection for a small peripheral lung ground-glass opacity nodule. A 66-year-old, female, nonsmoker had a persistent 1.2-cm right upper lobe ground-glass opacity nodule. Preoperative computed tomography-guided hookwire localization was performed, followed by video-assisted thoracic surgery right upper lobe wedge resection. The intraoperative pathology was adenocarcinoma in situ. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32758-8/fulltext.

and the detailed influence on quality of life and mental state should all be validated in prospective clinical trials. However, our results should arouse attention to incidental lung cancer in traditionally "low-risk" population because of the surprisingly high detection rate. Second, some employees with suspicious malignant nodules are still being followed up. However, the number of patients with pathologically confirmed lung cancer is already significant.

CONCLUSIONS

In conclusion, LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage with extremely good prognosis. There are challenges and opportunities for better understanding and management of this disease. A depiction of methods, results, and implications of this study is shown in the Graphical Abstract (Figure 3).

Conflict of Interest Statement

All authors have nothing to disclose with regard to commercial support.

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Key Words: low-dose computed tomography, lung cancer, young, female, nonsmokers, early-stage

APPENDIX E1

Results that support the increasing trend of young, female, nonsmoking, and early-stage lung cancer

METHODS

Patients

Lung cancer incidence, and mortality rate in Shanghai. The first dataset was lung cancer incidence, and mortality rate (age-standardized rate) between 2005 and 2014 from Shanghai Cancer Registry, which is a population-based cancer registry with quality data for more than 50 years, and covers 13 million people in Shanghai municipality.

Patients with lung cancer undergoing surgery in Fudan University Shanghai Cancer Center (FUSCC). The second dataset were a series of patients with primary lung cancer undergoing surgical resection in FUSCC from April 2008 to December 2017. The proportion of female, nonsmokers, patients ≤40 years old, and patients with stage 0/IA was calculated in each year. Nonsmokers were defined as patients who had never smoked cigarettes in their lifetime.

Patients with lung cancer receiving surgery in Seoul National University Bundang Hospital (SNUBH). The third dataset were a series of primary lung cancer patients receiving surgery in Seoul SNUBH in Korea from 2003 to 2017. The total number of patients, and the number of female, nonsmokers, patients ≤40 years old, and patients with stage 0/IA were recorded in each year.

Statistical Analysis

To characterize trends in lung cancer incidence and mortality rate over time, the average annual percent change (APC) and the corresponding 95% confidence interval (CI) were calculated using Joinpoint (version 4.1.1.3) by the National Cancer Institute (Bethesda, Md). The Cochrane Armitage trend test was used to determine if the proportion of the young, female, nonsmoking, or patients with stage 0/IA increased over the years. Statistical analysis was performed in R (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-tailed, and statistical significance was considered as $P < .05$.

RESULTS

Lung Cancer Incidence and Mortality Rate in Shanghai

In Shanghai, lung cancer incidence in men did not change significantly from 2005 to 2014 (APC, 0.76%; 95% CI, –0.27% to 1.80%, $P = .1255$), whereas lung cancer incidence in women increased significantly (APC, 5.50%; 95% CI, 2.94%-8.13%, $P = .0008$) (Figure E1). Patients were further stratified into categories according to age at diagnosis (25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years) (Table E1). In men, lung cancer incidence increased significantly only in 2 age groups (50-54 years and 55-59 years), whereas in women, lung cancer incidence increased significantly in all the age groups between 30 and 64 years old. Mortality rate of lung cancer showed a significantly decreasing trend from 2005 to 2014 in both men (APC, –1.71%; 95% CI, –2.98% to 0.04%, $P = .0152$) and women (APC, –1.96%; 95% CI, –3.84% to 0.04%, $P = .0461$) (Figure E1).

Patients With Lung Cancer Undergoing Surgery in FUSCC

Among 8355 patients with primary lung cancer undergoing surgical resection in FUSCC, the proportion of female (from 32.8% in 2008 to 55.7% in 2017, $P < .0001$), nonsmokers (from 43.9% in 2008 to 68.5% in 2017, $P < .0001$), patients ≤40 years old (from 2.2% in 2008 to 8.6% in 2017, $P < .0001$), and patients with stage 0/IA (from 32.2% in 2008 to 73.0% in 2017, $P < .0001$) increased significantly over the years (Figure E2).

Patients With Lung Cancer Receiving Surgery in SNUBH

Among 3536 patients with primary lung cancer receiving surgery in SNUBH in Korea, the proportion of female (from 14.3% in 2003 to 42.8% in 2017, $P < .0001$), nonsmokers (from 28.6% in 2003 to 43.0% in 2017, $P = .0001$), and patients with stage 0/IA (from 17.9% in 2003 to 45.1% in 2017, $P < .0001$) increased significantly from 2003 to 2017. The proportion of patients ≤40 years old did not change significantly over the years (0 in 2003 and 2.1% in 2017, $P = .8074$) (Figure E3).

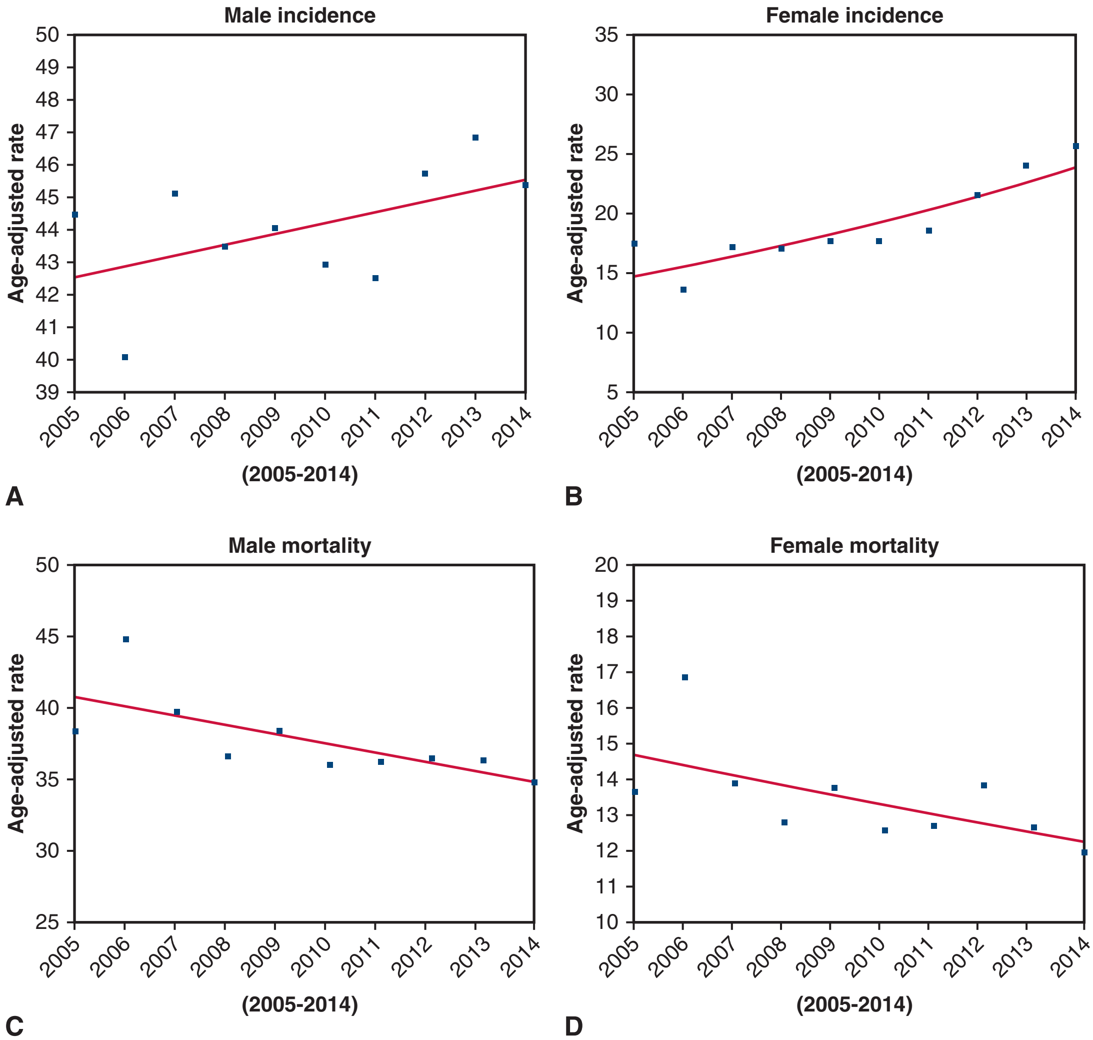

FIGURE E1. Incidence and mortality rate of lung cancer among male and female patients in Shanghai from 2005 to 2014. Lung cancer incidence in men did not change significantly from 2005 to 2014 (APC, 0.76%; 95% CI, –0.27% to 1.80%, $P = .1255$) (A), whereas lung cancer incidence in women increased significantly (APC, 5.50%; 95% CI, 2.94%-8.13%, $P = .0008$) (B). Mortality rate of lung cancer showed a significantly decreasing trend from 2005 to 2014 in both men (APC, –1.71%; 95% CI, –2.98% to 0.04%, $P = .015$) (C) and women (APC, –1.96%, 95% CI, –3.84% to 0.04%, $P = .046$) (D).

THOR

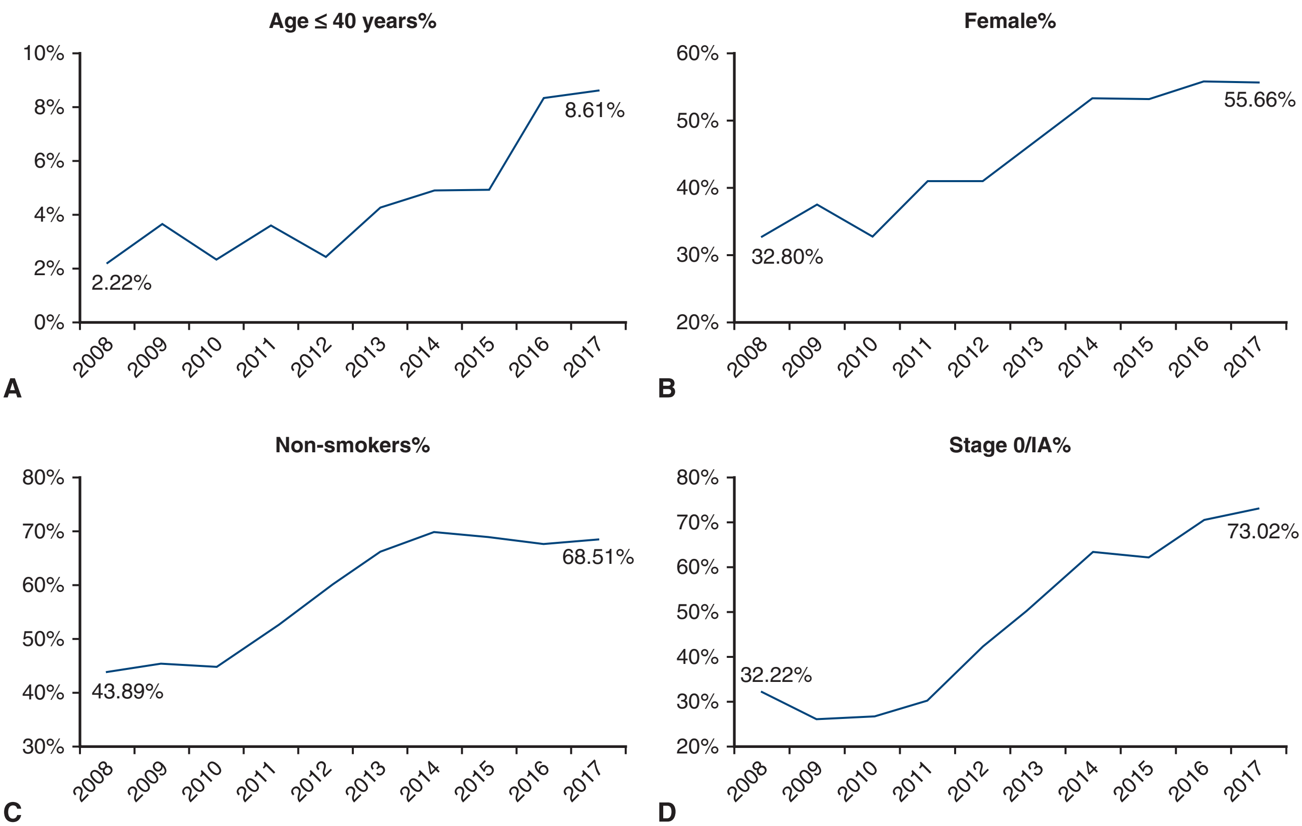

FIGURE E2. Proportion of patients ≤40 years old (A), female (B), nonsmokers (C), and patients with stage 0/IA (D) among 8355 patients with lung cancer undergoing surgery in Fudan University Shanghai Cancer Center from 2008 to 2017. The proportion of female (from 32.8% in 2008 to 55.7% in 2017), nonsmokers (from 43.9% in 2008 to 68.5% in 2017), patients ≤40 years old (from 2.2% in 2008 to 8.6% in 2017), and patients with stage 0/IA (from 32.2% in 2008 to 73.0% in 2017) increased significantly over the years.

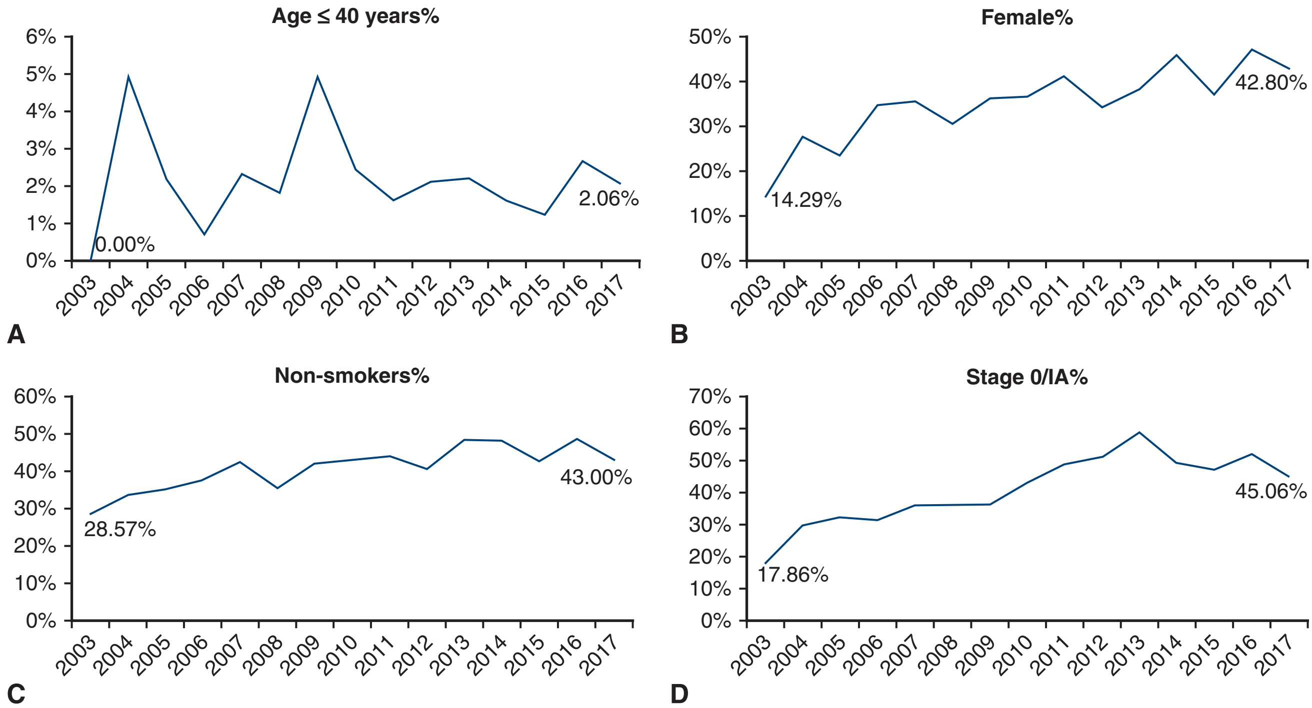

FIGURE E3. Proportion of patients ≤40 years old (A), female (B), nonsmokers (C), and patients with stage 0/IA (D) among 3536 patients with lung cancer undergoing surgery in Seoul National University Bundang Hospital from 2003 to 2017. The proportion of female (from 14.3% in 2003 to 42.8% in 2017), nonsmokers (from 28.6% in 2003 to 43.0% in 2017), and patients with stage 0/IA (from 17.9% in 2003 to 45.1% in 2017) increased significantly.

TABLE E1. Average APC of incidence and mortality rate of lung cancer in Shanghai among men and women from 2005 to 2014 stratified by age at diagnosis

	Age, y													
	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Overall
Incidence														
Male	12.92	7.03	1.59	–0.35	1.51	4.26*	6.58*	2.04	–0.35	-0.67	–1.75*	–1.77*	0.24	0.76
Female	34.48	15.00*	17.21*	10.21*	11.84*	10.10*	9.91*	6.52*	3.27	2.36*	NA	0.22	1.08	5.50*
Mortality														
Male	–23.4	–8.73	–10.57*	–8.73*	–4.98*	–0.37	1.52	–1.79	–3.26*	–2.08*	–2.12*	–0.73	2.83	–1.71*
Female	19.26	–2.61	–6.51*	–4.73	–4.09*	–2.95	–2.53	–1.73	–4.47*	–2.30*	–0.08	0.61	2.34*	–1.96*

The APC was calculated using Joinpoint (version 4.1.1.3) by the National Cancer Institute (Bethesda, Md). *Statistical significance.