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Increased risk of subsequent primary lung cancer among female hormone-related cancer patients: A meta-analysis based on over four million cases

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Abstract

Background: The incidence rate of lung cancer in women has significantly increased over the past decade, and previous evidence has indicated a significant relationship between the elevated levels of sex hormones and the risk of lung cancer. Therefore, we hypothesized that female hormone-related cancer (FHRC) patients, including breast, endometrial, cervical, and ovarian cancer patients, may experience a higher risk of developing subsequent lung cancer. This meta-analysis aimed to identify the risk of lung cancer among FHRC patients compared to the general population.

Methods: The PubMed, Web of Science, EMBASE, Cochrane Library, and CNKI databases were searched up to May 11, 2022. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were used to identify the risk of subsequent lung cancer after FHRC. Subgroup analyses based on the follow-up time and tumor type were also conducted.

Results: A total of 58 retrospective cohort studies involving 4,360,723 FHRC participants were included. The pooled results demonstrated that FHRC patients had a significantly increased risk of developing subsequent primary lung cancer (SIR = 1.61, 95% CI: 1.48–1.76, P <0.001). Subgroup analysis revealed an obvious trend of increasing lung cancer risk over time (SIRs for <5 years, ≥5 years, ≥10 years, ≥20 years, and ≥30 years after FHRC: 1.32, 1.59, 1.57, 1.68, and 1.95, respectively). In addition, subgroup analysis stratified by tumor type indicated an increased risk of developing subsequent lung cancer after breast (SIR = 1.25, P <0.001), endometrial (SIR = 1.40, P = 0.019), cervical (SIR = 2.56, P <0.001), and ovarian cancer (SIR = 1.50, P = 0.010).

Conclusion: FHRC patients are more likely to develop lung cancer than the general population. Furthermore, the increased risk of subsequent primary lung cancer is more obvious with a longer survival time and is observed in all types of hormone-related cancer.

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Keywords: Female hormone-related cancer; Risk; Subsequent primary lung cancer; Meta-analysis

Introduction

According to the latest cancer data, lung cancer is the second most common tumor and remains the leading cause of tumor-related death among women in the United States.[1] Moreover, the sex proportion and age distribution of lung cancer patients have changed significantly in the past decade, with obviously more young female patients than before.[1,2] In addition, breast cancer has become the most common cancer in the United States with a rising incidence, and the incidence rates of other female tumors, including uterine endometrial, uterine cervical, and ovarian cancers, have also been relatively high over the past few decades.[1,3,4] Overall, these four cancers are the leading causes of cancer burden in women, and they can be defined as female hormone-related cancers (FHRCs) to some extent due to their association with elevated levels of sex hormones, especially estrogen. Data suggest that there are more female lung cancer patients with previous FHRC than before in clinics.

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In recent years, increasing evidence has revealed the close relationship between sex hormones, especially estrogen, and carcinogenesis, tumor progression, and even therapeutic effects among female lung cancer patients.[5] Estrogens are overexpressed in tumors among some female lung adenocarcinoma patients and can activate several pathways in lung carcinogenesis, such as the cyclic adenosine monophosphate (cAMP), protein kinase B (Akt), phosphoinositide 3-kinase (PI3K), and extracellular regulated protein kinases (ERK) pathways.[6–9] Furthermore, estrogen promotes angiogenesis by activating vascular endothelial growth factor-A (VEGF-A) in endothelial cells.[10] In addition, a number of studies have indicated that hormone antagonism therapy is correlated with the decreased incidence rate of lung cancer, and demonstrated the obvious efficacy of estrogen antagonism in the treatment of lung cancer in women.[11,12] Overall, sex hormones play an essential role in the development and progression of female lung cancer.

In previous studies, we showed that female breast cancer patients were more likely to develop subsequent primary lung cancer than the general population, which was associated with the estrogen receptor and progesterone receptor status based on four million cases.[13] Moreover, the occurrence of secondary lung adenocarcinoma is closely related to several pathways, such as the PI3K-Akt, cAMP, and calcium ion signal pathways, and the expression levels of fibroblast growth factor-10 (FGF-10) and VEGF-A in female lung adenocarcinoma patients previous breast cancer are significantly higher than those in single primary lung adenocarcinoma patients.[14]

Thus, we hypothesized that FHRC patients may experience a higher risk of developing subsequent lung cancer than the general population, and the aim of this meta-analysis was to identify the risk for lung cancer among FHRC patients based on current evidence, which might help the clinical management of and screening for subsequent lung cancer in FHRC patients.

Methods

Registration

This study was registered with International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (https://inplasy.com/, No. INPLASY2022 70044).

Literature retrieval

The PubMed, EMBASE, Web of Science, Cochrane Library, and CNKI electronic databases were searched from inception to May 11, 2022, for relevant studies. The following keywords were applied during the literature search: tumor, cancer, neoplasm, carcinoma, lung, pulmonary, breast cancer, breast carcinoma, cervical cancer, cervical carcinoma, carcinoma of cervix, endometrial cancer, endometrial carcinoma, carcinoma of endometrium, ovarian cancer, ovarian carcinoma, ovary cancer, ovary carcinoma, carcinoma of ovary, second primary, and subsequent primary. A combination of subject terms and free words was also used. The detailed search strategy in PubMed is presented in Supplementary Figure 1, http://links.lww.com/CM9/B994. In addition, all the references cited in the included studies and relevant review publications were also reviewed for possible inclusion.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) female patients pathologically diagnosed with primary breast, endometrial, cervical, or ovarian cancer; (2) studies comparing the incidence rate of lung cancer between FHRC patients and the general population; (3) patients with primary lung cancer diagnosed pathologically; (4) studies that reported standardized incidence ratios (SIRs) with 95% confidence interval (CIs) or enough data to calculate them; (5) studies that used lung cancer incidence rates of the whole population in the research area or healthy people that were matched for at least age as controls during the calculation of SIRs and 95% CIs; (6) cohort studies or case-controlled studies; (7) studies with available full text.

The exclusion criteria were as follows: (1) duplicated or severely overlapped (overlapped period >50%) data; (2) meeting abstracts, reviews, letters, editorials, or case reports; (3) studies for which the SIRs and corresponding 95% CIs were not available even after contacting the authors; (4) studies involving patients with other thoracic malignancies such as mediastinal and pleural tumors; and (5) case-controlled studies with a total sample size of less than 1000 cases.

Literature selection and data collection

First, duplicated publications were removed with EndNote (version X9, Clarivate Analytics, London, England, United Kingdom) automatically or manually. Then, the titles and abstracts were reviewed for relevance, and full texts of potentially relevant studies were further reviewed for availability according to the inclusion and exclusion criteria.

In this meta-analysis, the following information was collected from the included studies: the name of the first author, publication year, sample size, database or region of the included cases, diagnosis year of FHRC, tumor type, follow-up period, treatment (chemotherapy and radiotherapy), patient age at FHRC diagnosis, degree of FHRC (invasive *vs. in situ*), source of SIR, and SIR and corresponding 95% CI.

Quality assessment of the included studies

All included studies were retrospective cohort studies. Thus, the Newcastle–Ottawa scale (NOS) was applied for quality assessment, and studies with an NOS score of six or higher were defined as high-quality studies.[15]

The literature search, study selection, data extraction, and quality assessment were all performed by two authors independently, and any disagreement was resolved by team discussion.

Statistical analysis

All statistical analyses were performed with STATA (version 15.0, StataCorp LLC, College Station, Texas, USA) software. The SIRs and 95% CIs were used to determine the risk for subsequent primary lung cancer among FHRC patients compared to the general population. The heterogeneity among the included studies was assessed by I^2 statistics and Q tests. If significant heterogeneity was detected, according to an I^2 >50% or P <0.1, the random-effects model was applied; otherwise, the fixed-effects model was used.[16] In addition, subgroup analysis based on the tumor type, follow-up period, treatment, patient age at FHRC diagnosis, and source of SIR and sensitivity analyses for breast, endometrial, cervical, and ovarian cancer patients and all FHRC patients were conducted to identify the source of heterogeneity and stability of pooled results in this meta-analysis. Furthermore, Begg's funnel plot and Egger's test were conducted to detect publication bias.[17] If significant publication bias was observed, then the trim-and-fill method would be applied to evaluate the influence of potentially unpublished papers on the stability of pooled results.[13] A P-value <0.05 was regarded as a significant difference.

Results

Literature search and selection

Initially, 6874 records were identified from the four databases, and 1886 duplicated records were removed. After screening the titles and abstracts, 4871 irrelevant publications were deleted. Then, the full texts of 117 publications were carefully reviewed for eligibility, and 59 publications were excluded due to insufficient data (n = 34), overlapping data (n = 14), duplicated data (n = 6), or a combination with other thoracic tumors (n = 5). Finally, a total of 58 studies were included in this meta-analysis.[18–75] The specific literature selection process is shown in Figure 1.

Basic characteristics of the included studies

Among the 58 included studies, 4,360,723 patients were enrolled, with sample sizes ranging from 763 to 525,527 and publication years ranging from 1974 to 2021. In addition, 32,[18,21,28,33,35,36,38,39,41,43–51,53,55–60,62,64,67,68,70,72,75] 11,[28,29,32,42,52,55,59,61,65,71,74] 19,[18–20,23,25–27,29–32,34,37,40,53,54,63,70,73] and 8[22,24,29,32,55,66,69,70] studies reported the risk of developing secondary lung cancer after breast, endometrial, cervical, and ovarian cancer, respectively. Additionally, 47 studies reported the SIRs and 95% CIs directly,[21,24,26,29–32,34–47,49–52,54–75] and the other 11 studies provided relevant data.[18–20,22,23,25,27,28,33,48,53] Furthermore, all studies were high-quality studies with NOS scores of six or higher. Other detailed information is presented in Table 1.

Risk of developing primary lung cancer among FHRC patients

After combining the 58 included studies,[18–75] the pooled results demonstrated that FHRC patients had a much higher risk of developing primary lung cancer than the general population (SIR = 1.61, 95% CI: 1.48–1.76, P <0.001; I^2 = 97.6%, $P_{heterogeneity}$ <0.001) [Table 2].

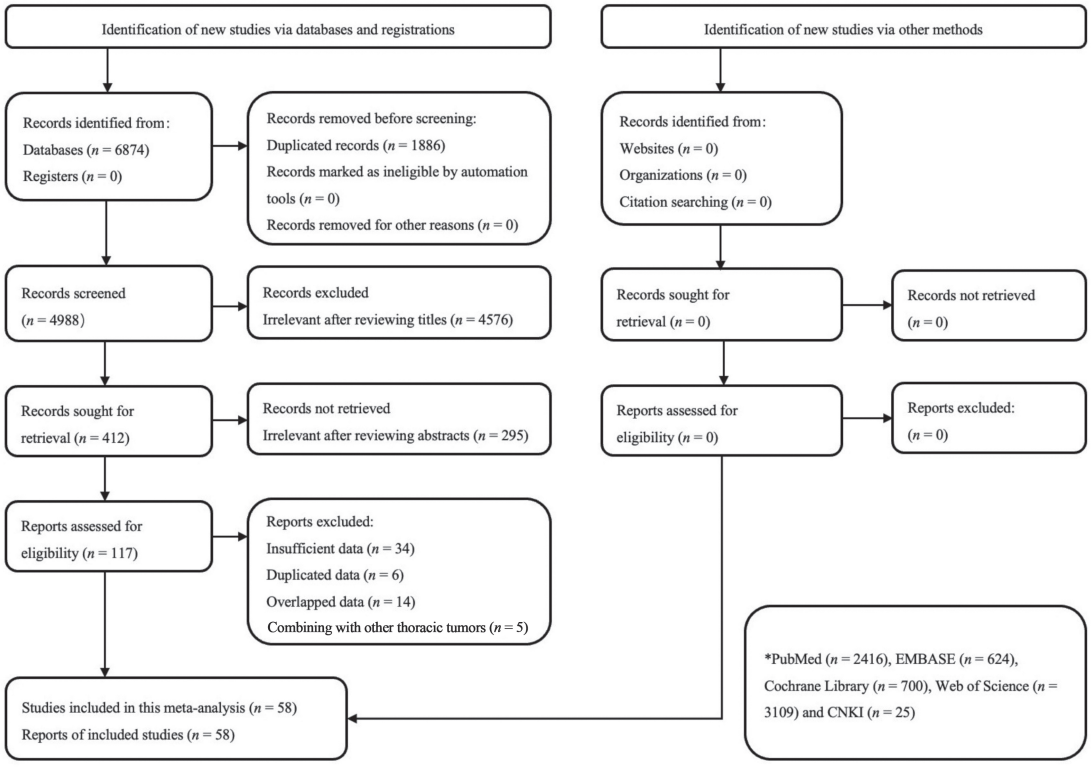

Figure 1: The flow diagram of this meta-analysis.

Table 1: Basic characteristics of included studies.

Author	Publication year	Sample size	Database or region	Diagnosis year of FHRC	Tumor type	R/E	NOS
Newell *et al*[18]	1974	7874	CHLTR	NR	Breast, cervix	E	6
Kapp *et al*[19]	1982	763	YUMC	1953–1972	Cervix	E	6
Clarke *et al*[20]	1984	7535	OCTRF and OCI	1960–1975	Cervix	E	7
Storm *et al*[21]	1986	208,192	DCR	1943–1980	Breast	R	8
Kaldor *et al*[22]	1987	87,219	7 countries	1945–1984	Ovary	E	7
Storm *et al*[23]	1988	44,440	DCR	1943–1982	Cervix	E	7
Prior and Pope[24]	1989	7203	BWMCR	1957–1976	Ovary	R	7
Arai *et al*[25]	1991	11,855	NIRS, NCCH, CIH, SUH	1961–1981	Cervix	E	7
Rabkin *et al*[26]	1992	25,295	CTR	1935–1988	Cervix	R	7
Levi *et al*[27]	1993	34,615	VCR	1974–1989	Cervix	E	7
Tsukuma *et al*[28]	1994	217,307	Osaka	1966–1986	Breast, endometrium	E	8
Bergfeldt *et al*[29]	1995	15,200	SGCR	1958–1992	Cervix, endometrium, ovary	R	7
Bjorge *et al*[30]	1995	37,001	Norway	1990–1992	Cervix	R	7
Kleinerman *et al*[31]	1995	86,193	13 cancer registries from 5 countries	1935–1990	Cervix	R	7
McCredie *et al*[32]	1996	17,378	New South Wales (Australia)	1972–1991	Cervix, endometrium, ovary	R	7
Buiatti *et al*[33]	1997	5237	TTR, RCR, CRR	1981–1989	Breast	E	7
Fisher *et al*[34]	1997	4457	MTR	1985–1987	Cervix	R	7
Volk and PompeKirn[35]	1997	8917	SCR*	1961–1985	Breast	R	7
Dorffel *et al*[36]	2000	5485	NCI	1976–1988	Breast	R	7
Hemminki *et al*[37]	2000	135,386	SFCD	1958–1996	Cervix	R	8
Tanaka *et al*[38]	2001	2786	OMC	1970–1994	Breast	R	7
Rubino *et al*[39]	2002	4171	IGR	1954–1984	Breast	R	7
Evans *et al*[40]	2003	21,605	TCR*	1960–1999	Cervix	R	7
Levi *et al*[41]	2003	9729	SCR***	1974–1998	Breast	R	7
Li and Hemminki[42]	2003	4524	SFCD	1961–1998	Endometrium	R	7
Roychoudhuri *et al*[43]	2004	64,782	TCR*	1961–2000	Breast	R	7
Soerjomataram *et al*[44]	2005	9919	ECR	1972–2000	Breast	R	7
Levi *et al*[45]	2006	6111	SVCR	1978–1998	Breast	R	7
Mellemkjaer *et al*[46]	2006	525,527	13 cancer registries	1943–2000	Breast	R	8
Prochazka *et al*[47]	2006	152,586	SCR**	1958–2000	Breast	R	8
Brown *et al*[48]	2007	376,825	Denmark, Finland, Sweden	1943–2002	Breast	E	8
Lee *et al*[49]	2008	53,783	Taiwan, China	1979–2003	Breast	R	7
Schaapveld *et al*[50]	2008	58,068	CCCN, CCCA, CCCS	1989–2003	Breast	R	7
Rosso *et al*[51]	2009	9233	Turin	1985–1998	Breast	R	7
Brown *et al*[52]	2010	69,739	SEER	1973–2005	Endometrium	R	7
Berrington de Gonzalez *et al*[53]	2011	247,077	SEER	1973–2002	Breast, cervix	E	8
Chen *et al*[54]	2012	52,972	TCR**	1979–2008	Cervix	R	7
Tabuchi *et al*[55]	2012	355,966	OCR	1985–2004	Breast, endometrium, ovary	R	8
Grantzau *et al*[56]	2013	46,176	DBCG	1982–2007	Breast	R	7
Valuckas *et al*[57]	2013	832	VUOI	1987–1996	Breast	R	6
Yi *et al*[58]	2013	4198	ACC	1979–2007	Breast	R	7
Utada *et al*[59]	2014	174,477	NPCR	1985–2007	Breast, endometrium	R	8
Hamilton *et al*[60]	2015	12,836	British Columbia	1989–2005	Breast	R	7
Lee *et al*[61]	2015	11,571	TCR**	1979–2008	Endometrium	R	7
Lim *et al*[63]	2016	72,805	KCCR	1993–2010	Cervix	R	7
Lu *et al*[64]	2016	67,134	Taiwan, China	2000–2011	Breast	R	7
Bazire *et al*[62]	2016	17,745	CI	1981–2000	Breast	R	7
Chen *et al*[65]	2017	65,575	German and Swedish datasets	1997–2012	Endometrium	R	7
Kanninen *et al*[66]	2017	41,073	SEER	1992–2012	Ovary	R	7
Silverman *et al*[67]	2017	46,090	INCR	1992–2006	Breast	R	7
Lin *et al*[68]	2018	88,446	Taiwan, China	2000–2011	Breast	R	7
Zheng *et al*[69]	2018	11,300	SFCD	1958–2015	Ovary	R	7
Bright *et al*[70]	2019	64,402	ONS, WCR	1971–2006	Breast, cervix, ovary	R	7
Rhoades *et al*[71]	2019	96,256	SEER	1992–2014	Endometrium	R	7
Zheng *et al*[72]	2019	87,752	SFCD	1958–2015	Breast	R	7
Sung *et al*[73]	2020	20,153	SEER	1992–2011	Cervix	R	7

(*Continued*)

Table 1

(Continued)

Author	Publication year	Sample size	Database or region	Diagnosis year of FHRC	Tumor type	R/E	NOS
Lai *et al*[74]	2021	7725	TCR**	1995–2013	Endometrium	R	7
Sung *et al*[75]	2021	431,222	SEER	1992–2015	Breast	R	8

ACC: Anderson Cancer Center; BWMCR: Birmingham and West Midlands Cancer Registry; CCCA: Comprehensive Cancer Center Amsterdam; CCCN: Comprehensive Cancer Center-North Netherlands; CCCS: Comprehensive Cancer Center South; CHLTR: Charity Hospital of Louisiana Tumor Registry; CI: Curie Institute; CIH: Cancer Institute Hospital; CRR: Cancer Registry of Romagna; CTR: Connecticut Tumor Registry; DBCG: Danish Breast Cancer Cooperative Group; DCR: Danish Cancer Registry; E: Estimated; ECR: Eindhoven cancer registry; FHRC: Female hormone-related cancer; IGR: Institut Gustave Roussy; INCR: Israel National Cancer Registry; KCCR: Korea Central Cancer Registry; MTR: Michigan Tumor Registry; NCCH: National Cancer Center Hospital; NCI: National Cancer Institute; NIRS: National Institute of Radiological Sciences Hospital; NOS: Newcastle–Ottawa scale; NPCR: Nagasaki Prefecture Cancer Registry; NR: Not reported; OCI: Ontario Cancer Institute; OCR: Osaka Cancer Registry; OCTRF: Ontario Cancer Treatment and Research Foundation; OMC: Osaka Medical Center; ONS: Office for National Statistics; R: Reported; RCR: Ragusa Cancer Registry; SCR***: Swiss Cancer Registries; SCR**: Swedish Cancer Registry; SCR*: Slovenia Cancer Registry; SEER: Surveillance, Epidemiology, and End Results; SFCD: Swedish Family-Cancer Database; SGCR: Stockholm-Gotland Cancer Register; SUH: Shinshu University Hospital; SVCR: Swiss Vaud Cancer Registry; TCR**: Taiwan (China) Cancer Registry; TCR*: Thames Cancer Registry; TTR: Tuscany Tumour Registry; VCR: Vaud Cancer Registry; VUOI: Vilnius University Oncology Institute; WCR: Welsh Cancer registry; YUMC: Yale University Medical Center.

Subgroup analysis based on the follow-up period was then conducted. Among FHRC patients who were followed up for less than 5 years, the risk for lung cancer was not significantly increased (SIR = 1.32, 95% CI: 0.90–1.92, $P = 0.154$) [Supplementary Figure 2A, http://links.lww.com/CM9/B994]. However, for patients who were followed up for ≥5 years, ≥10 years, ≥20 years, and ≥30 years, an increased risk of developing subsequent lung cancer was observed (SIR = 1.59, 95% CI: 1.39–1.82, $P < 0.001$; SIR = 1.57, 95% CI: 1.33–1.85, $P < 0.001$; SIR = 1.68, 95% CI: 1.19–2.37, $P = 0.003$; SIR = 1.95, 95% CI: 1.50–2.52, $P < 0.001$) [Supplementary Figure 2B–E, http://links.lww.com/CM9/B994]. Moreover, the risk for subsequent primary lung cancer increased over time. The results of subgroup analysis based on treatment showed that only FHRC patients who received chemotherapy exhibited an increased risk for primary lung cancer (SIR = 1.73, 95% CI: 1.05–2.87, $P = 0.032$) [Supplementary Figure 2F–I, http://links.lww.com/CM9/B994]. Furthermore, subgroup analyses stratified by age, degree of malignancy and source of SIR showed that none of these parameters had a significant impact on the risk of developing lung cancer among FHRC patients (age <50 years: SIR = 2.55, 95% CI: 1.95–3.34, $P < 0.001$; age ≥50 years: SIR = 1.21, 95% CI: 1.08–1.36, $P = 0.001$; invasive: SIR = 2.25, 95% CI: 1.72–2.94, $P < 0.001$; *in situ*: SIR = 2.18, 95% CI: 2.03–2.33, $P < 0.001$; reported SIR: SIR = 1.50, 95% CI: 1.36–1.66, $P < 0.001$; estimated SIR: SIR = 2.08, 95% CI: 1.73–2.50, $P < 0.001$) [Supplementary Figure 2J–O, http://links.lww.com/CM9/B994]. Notably, the increased risk for subsequent primary lung cancer in younger FHRC patients was much more obvious than that in older FHRC patients [Table 2].

Table 2: Overall results of meta-analysis.

Items	No. of studies	SIR	95% CI	*P*-value	I^2 (%)	$P_{heterogeneity}$
Overall	58[18–75]	1.61	1.48–1.76	<0.001	97.6	<0.001
Follow-up period						
<5 years	13[29,30,33,35,38,43,49,54,61,63,65,66,68]	1.32	0.90–1.92	0.154	96.4	<0.001
≥5 years	21[24,29–31,33,35,37–39,41,43,46,49,52,54,57,61,63,65,66,70]	1.59	1.39–1.82	<0.001	94.1	<0.001
≥10 years	16[24,29–31,35,37–39,43,46,49,52,57,61,66,70]	1.57	1.33–1.85	<0.001	94.6	<0.001
≥20 years	5[30,31,35,52,70]	1.68	1.19–2.37	0.003	94.0	<0.001
≥30 years	2[31,70]	1.95	1.50–2.52	<0.001	50.8	0.107
Treatment						
Radiotherapy	11[21,24,31,43,45,52,53,56,57,60,62]	1.29	0.97–1.70	0.078	97.9	<0.001
Non-radiotherapy	10[21,24,31,43,45,52,53,56,62,74]	1.10	0.89–1.35	0.379	95.0	<0.001
Chemotherapy	3[24,38,62]	1.73	1.05–2.87	0.032	0	0.494
Non-chemotherapy	3[24,62,74]	1.67	0.84–3.34	0.142	91.3	<0.001
Age at FHRC diagnosis						
<50 years	14[35,36,38,39,44,46,47,49,54,61,63,68,74,75]	2.55	1.95–3.34	<0.001	95.2	<0.001
≥50 years	15[35,36,38,39,44,46,47,49,54,61,63,66,68,74,75]	1.21	1.08–1.36	0.001	93.6	<0.001
Degree of FHRC						
Invasive	12[19,20,23,26,31,34,37,40,53,54,63,73]	2.25	1.72–2.94	<0.001	99.0	<0.001
In situ	3[23,30,37]	2.18	2.03–2.33	<0.001	0	0.948
Source of SIR						
Reported	47[21,24,26,29–32,34–47,49–52,54–75]	1.50	1.36–1.66	<0.001	97.7	<0.001
Estimated	11[18–20,22,23,25,27,28,33,48,53]	2.08	1.73–2.50	<0.001	96.7	<0.001

CI: Confidence interval; FHRC: Female hormone-related cancer; SIR: Standard incidence ratio.

Risk of developing primary lung cancer among breast cancer patients

A total of 32 included studies involving 3,298,285 cases reported the difference in the incidence rate of lung cancer between female breast cancer patients and the general population.[18,21,28,33,35,36,38,39,41,43–51,53,55–60,62,64,67,68,70,72,75] The pooled results demonstrated that female breast cancer patients had a 25% increased risk of developing lung cancer (SIR = 1.25, 95% CI: 1.16–1.35, P <0.001; I^2 = 95.1%, $P_{heterogeneity}$ <0.001) [Supplementary Figure 3A, http://links.lww.com/CM9/B994].

Subgroup analysis based on the follow-up period showed that except for patients with a follow-up time of less than 5 years, other breast cancer patients had a higher risk for lung cancer than the general population (≥5 years: SIR = 1.49, 95% CI: 1.23–1.81, P <0.001; ≥10 years: SIR = 1.55, 95% CI: 1.25–1.93, P <0.001; ≥20 years: SIR = 2.39, 95% CI: 1.66–3.45, P <0.001; ≥30 years: SIR = 1.77, 95% CI: 1.34–2.33, P <0.001) [Supplementary Figure 3B–D, http://links.lww.com/CM9/B994]. According to the treatment strategy, breast cancer patients who did not receive radiotherapy showed a decreased risk of developing lung cancer [Supplementary Figure 3E, http://links.lww.com/CM9/B994]. In addition, patients who were younger or older than 50 years had a significantly higher risk for lung cancer (SIR = 1.99, 95% CI: 1.60–2.48, P <0.001; SIR = 1.08, 95% CI: 1.02–1.14, P = 0.012) [Supplementary Figure 3F–G, http://links.lww.com/CM9/B994]. Furthermore, after combining studies reporting the SIRs with 95% CIs directly, an increased risk of lung cancer among breast cancer patients was also observed (SIR = 1.27, 95% CI: 1.16–1.39, P <0.001) [Supplementary Figure 3H, http://links.lww.com/CM9/B994]. Other detailed results are presented in Table 3.

Risk of developing primary lung cancer among endometrial cancer patients

Eleven studies involving 1,013,469 participants compared the incidence rates of lung cancer between endometrial cancer patients and the general population.[28,29,32,42,52,55,59,61,65,71,74] The pooled results showed that endometrial cancer patients had a 40% increased risk of developing lung cancer (SIR = 1.40, 95% CI: 1.06–1.86, P = 0.019; I^2 = 97.2%, $P_{heterogeneity}$ <0.001) [Supplementary Figure 4A, http://links.lww.com/CM9/B994].

Similarly, subgroup analyses stratified by the follow-up period, treatment, patient age, and source of SIR were conducted. However, an opposite phenomenon was found among endometrial cancer patients who were followed up for over 10 years (SIR = 0.69, 95% CI: 0.64–0.75, P <0.001) [Supplementary Figure 4B, http://links.lww.com/CM9/B994] and 20 years (SIR = 0.67, 95% CI: 0.56–0.79, P = 0.001) [Supplementary Figure 4C, http://links.lww.com/CM9/B994] and received radiotherapy (SIR = 0.88, 95% CI: 0.79–0.99, P = 0.028). Subgroup analyses based on the age and source of SIR indicated a significantly increased risk of developing lung cancer (age <50 years: SIR = 3.99, 95% CI: 1.08–14.77, P = 0.038; age ≥50 years: SIR = 1.80, 95% CI: 1.48–2.17, P <0.001; reported SIR: SIR = 1.35, 95% CI: 1.01–1.80, P = 0.044; estimated SIR: SIR = 2.20, 95% CI: 1.56–3.10, P <0.001) [Supplementary Figure 4D–F, http://links.lww.com/CM9/B994] [Table 3].

Unlike overall FHRC and breast cancer patients, endometrial cancer patients had a reduced risk of developing lung cancer over time [Table 3]. However, younger patients were indeed more likely to develop subsequent primary lung cancer, as mentioned above.

Risk of developing primary lung cancer among cervical cancer patients

Nineteen relevant studies involving 614,519 patients were included in this part of the meta-analysis.[18–20,23,25–27,29–32,34,37,40,53,54,63,70,73] The pooled results after combining these 19 studies showed that cervical cancer patients had an increased risk of developing lung cancer compared with the general population (SIR = 2.56, 95% CI: 2.33–2.80, P <0.001; I^2 = 86.9%, $P_{heterogeneity}$ <0.001) [Supplementary Figure 5A, http://links.lww.com/CM9/B994].

All subgroup analyses based on the follow-up period (<5 years: SIR = 3.07, 95% CI: 1.38–6.80, P = 0.006; ≥5 years: SIR = 2.28, 95% CI: 1.98–2.61, P <0.001; ≥10 years: SIR = 2.18, 95% CI: 1.94–2.45, P <0.001; ≥20 years: SIR = 1.93, 95% CI: 1.49–2.51, P <0.001; ≥30 years: SIR = 2.06, 95% CI: 1.38–3.06, P <0.001) [Supplementary Figure 5B–F, http://links.lww.com/CM9/B994], treatment (radiotherapy: SIR = 2.66, 95% CI: 2.08–3.41, P <0.001; non-radiotherapy: SIR = 1.75, 95% CI: 1.11–2.74, P = 0.015) [Supplementary Figure 5G–H, http://links.lww.com/CM9/B994], patient age (<50 years: SIR = 4.09, 95% CI: 3.21–5.20, P <0.001; ≥50 years: SIR = 1.80, 95% CI: 1.66–1.94, P <0.001) [Supplementary Figure 5I, J, http://links.lww.com/CM9/B994], degree of malignancy (invasive: SIR = 2.48, 95% CI: 2.19–2.80, P <0.001; *in situ*: SIR = 2.18, 95% CI: 2.03–2.33, P <0.001) [Supplementary Figure 5K, L, http://links.lww.com/CM9/B994], and source of SIR (reported: SIR = 2.50, 95% CI: 2.27–2.75, P <0.001; estimated: SIR = 2.85, 95% CI: 2.27–3.57, P <0.001) [Supplementary Figure 5M, N, http://links.lww.com/CM9/B994] indicated an increased risk of developing lung cancer among cervical cancer patients [Table 3]. Similarly, this phenomenon was more pronounced in younger patients.

Risk of developing primary lung cancer among ovarian cancer patients

Only eight studies involving 517,876 cases were enrolled.[22,24,29,32,55,66,69,70] The pooled results also demonstrated that ovarian cancer patients showed a significantly increased risk of developing lung cancer (SIR = 1.50, 95% CI: 1.10–2.05, P = 0.010; I^2 = 87.6%, $P_{heterogeneity}$ <0.001) [Supplementary Figure 6A, http://links.lww.com/CM9/B994].

Subgroup analysis based on the follow-up period indicated that ovarian cancer patients had a decreased risk for developing lung cancer within 5 years after the diagnosis of ovarian carcinoma (SIR = 0.67, 95% CI: 0.52–0.86, P =

Table 3: Detailed results of meta-analysis for specific cancer.

Items	No. of studies	SIR	95% CI	*P*-value	I^2 (%)	$P_{heterogeneity}$
Breast cancer	32[18,21,28,33,35,36,38,39,41,43–51,53,55–60,62,64,67,68,70,72,75]	1.25	1.16–1.35	<0.001	95.1	<0.001
Follow-up period						
<5 years	6[33,35,38,43,49,68]	1.17	0.81–1.69	0.401	85.1	<0.001
≥5 years	10[33,35,38,39,41,43,46,49,57,70]	1.49	1.23–1.81	<0.001	88.6	<0.001
≥10 years	8[35,38,39,43,46,49,57,70]	1.55	1.25–1.93	<0.001	88.2	<0.001
≥20 years	2[35,70]	2.39	1.66–3.45	<0.001	73.6	0.022
≥30 years	1[70]	1.77	1.34–2.33	<0.001	–	–
Treatment						
Radiotherapy	8[21,43,45,53,56,57,60,62]	1.13	0.98–1.32	0.098	82.1	<0.001
Non-radiotherapy	6[21,43,45,53,56,62]	0.86	0.78–0.96	0.006	51.9	0.023
Chemotherapy	2[38,62]	1.49	0.84–2.63	0.173	0	0.365
Non-chemotherapy	1[62]	0.98	0.48–2.00	0.949	71.6	0.061
Age						
<50 years	10[35,36,38,39,44,46,47,49,68,75]	1.99	1.60–2.48	<0.001	88.3	<0.001
≥50 years	10[35,36,38,39,44,46,47,49,68,75]	1.08	1.02–1.14	0.012	58.2	0.008
Degree of malignancy						
Invasive	1[53]	0.98	0.76–1.25	0.852	97.8	<0.001
Source of SIR						
Reported	27[21,35,36,38,39,41,43–47,49–51,55–60,62,64,67,68,70,72,75]	1.27	1.16–1.39	<0.001	94.8	<0.001
Estimated	5[18,28,33,48,53]	1.15	0.94–1.41	0.178	96.0	<0.001
Endometrial cancer	11[28,29,32,42,52,55,59,61,65,71,74]	1.40	1.06–1.86	0.019	97.2	<0.001
Follow-up period						
<5 years	3[29,61,65]	1.31	0.74–2.32	0.352	92.9	<0.001
≥5 years	4[29,52,61,65]	0.91	0.70–1.18	0.465	90.7	<0.001
≥10 years	3[29,52,61]	0.69	0.64–0.75	<0.001	0	0.583
≥20 years	1[52]	0.67	0.56–0.79	0.001	18.5	0.268
Treatment						
Radiotherapy	1[52]	0.88	0.79–0.99	0.028	–	–
Non-radiotherapy	2[52,74]	1.68	0.32–8.87	0.543	99.3	<0.001
Non-chemotherapy	1[74]	3.94	3.06–5.08	<0.001	–	–
Age						
<50 years	2[61,74]	3.99	1.08–14.77	0.038	87.7	0.004
≥50 years	2[61,74]	1.80	1.48–2.17	<0.001	0	0.439
Source of SIR						
Reported	10[29,32,42,52,55,59,61,65,71,74]	1.35	1.01–1.80	0.044	97.3	<0.001
Estimated	1[28]	2.20	1.56–3.10	<0.001	–	–
Cervix cancer	19[18–20,23,25–27,29–32,34,37,40,53,54,63,70,73]	2.56	2.33–2.80	<0.001	86.9	<0.001
Follow-up period						
<5 years	4[29,30,54,63]	3.07	1.38–6.80	0.006	97.8	<0.001
≥5 years	6[30,31,37,54,63,70]	2.28	1.98–2.61	<0.001	86.5	<0.001
≥10 years	5[29–31,37,70]	2.18	1.94–2.45	<0.001	68.0	<0.001
≥20 years	3[30,31,70]	1.93	1.49–2.51	<0.001	73.9	0.001
≥30 years	2[31,70]	2.06	1.38–3.06	<0.001	63.5	0.065
Treatment						
Radiotherapy	2[31,53]	2.66	2.08–3.41	<0.001	91.9	<0.001
Non-radiotherapy	2[31,53]	1.75	1.11–2.74	0.015	93.7	<0.001
Age						
<50 years	2[54,63]	4.09	3.21–5.20	<0.001	78.2	0.032
≥50 years	2[54,63]	1.80	1.66–1.94	<0.001	0	0.930
Degree of malignancy						
Invasive	12[19,20,23,26,31,34,37,40,53,54,63,73]	2.48	2.19–2.80	<0.001	90.6	<0.001
In situ	3[23,30,37]	2.18	2.03–2.33	<0.001	0	0.948
Source of SIR						
Reported	12[26,29–32,34,37,40,54,63,70,73]	2.50	2.27–2.75	<0.001	86.8	<0.001
Estimated	7[18–20,23,25,27,53]	2.85	2.27–3.57	<0.001	87.7	<0.001
Ovary cancer	8[22,24,29,32,55,66,69,70]	1.50	1.10–2.05	0.010	87.6	<0.001
Follow-up period						
<5 years	2[29,66]	0.67	0.52–0.86	0.002	0	0.823

(*Continued*)

Table 3
(Continued)

Items	No. of studies	SIR	95% CI	*P*-value	I^2 (%)	$P_{heterogeneity}$
≥5 years	3[24,29,66]	1.57	0.91–2.73	0.108	77.5	0.001
≥10 years	3[24,29,66]	1.95	0.85–4.48	0.113	81.3	<0.001
Treatment						
Radiotherapy	1[24]	1.65	0.64–4.21	0.298	0	0.892
Non-radiotherapy	1[24]	2.48	1.32–4.65	0.005	0	0.491
Chemotherapy	1[24]	2.98	1.02–8.65	0.045	0	0.578
Non-chemotherapy	1[24]	1.98	1.11–3.53	0.021	0	0.616
Age						
≥50 years	1[66]	0.69	0.56–0.86	0.001	–	–
Source of SIR						
Reported	7[24,29,32,55,66,69,70]	1.57	1.07–2.30	0.022	89.1	<0.001
Estimated	1[22]	1.20	0.99–1.46	0.068	–	–

CI: Confidence interval; SIR: Standard incidence ratio. –: Not available.

0.002) [Supplementary Figure 6B, http://links.lww.com/CM9/B994], but a trend of increased risk of developing lung cancer was observed with a longer follow-up period (≥5 years: SIR = 1.57, 95% CI: 0.91–2.73, *P* = 0.108; ≥10 years: SIR = 1.95, 95% CI: 0.85–4.48, *P* = 0.113) [Table 3]. Moreover, among ovarian cancer patients who did not receive radiotherapy (SIR = 2.48, 95% CI: 1.32–4.65, *P* = 0.005) or chemotherapy (SIR = 1.98, 95% CI: 1.11–3.53, *P* = 0.021) and received chemotherapy (SIR = 2.98, 95% CI: 1.02–8.65, *P* = 0.045), positive findings were revealed [Supplementary Figure 6C–E, http://links.lww.com/CM9/B994]. For patients who were older than 50 years, a decreased incidence rate of lung cancer was observed (SIR = 0.69, 95% CI: 0.56–0.86, *P* = 0.001). In addition, after combining the data of studies that reported the SIRs with 95% CIs directly, an increased risk of developing primary lung cancer was also detected (SIR = 1.57, 95% CI: 1.07–2.30, *P* = 0.022) [Supplementary Figure 6F and Table 3, http://links.lww.com/CM9/B994].

Sensitivity analysis and publication bias

Sensitivity analyses for all FHRC, breast, endometrial, cervical, and ovarian cancer patients were conducted [Supplementary Figure 7A–E, http://links.lww.com/CM9/B994]. Overall, most of the results of this meta-analysis were stable and reliable, except for the endometrial cancer [Supplementary Figure 7C, http://links.lww.com/CM9/B994]. Therefore, more studies are still needed to verify our findings.

Similarly, publication bias for all FHRC (*P* = 0.001), breast (*P* = 0.155), endometrial (*P* = 0.004), cervical (*P* = 0.173), and ovarian cancer (*P* = 0.138) patients was assessed [Supplementary Figure 8A–E, http://links.lww.com/CM9/B994], indicating that there was significant publication bias for the association of FHRC and endometrial cancer with increased risk of lung cancer. Therefore, the trim-and-fill method was applied. However, no potentially unpublished studies were detected according to the filled funnel plots [Supplementary Figure 8F–G, http://links.lww.com/CM9/B994].

Discussion

In the current meta-analysis, we demonstrated that FHRC patients experienced a significantly increased risk of developing subsequent primary lung cancer after evaluating 58 relevant cohort studies involving 4,360,723 participants. In addition, subgroup analyses indicated an obvious trend of increasing lung cancer risk over time, and an increased risk for secondary lung cancer was observed for every type of FHRC. However, it was associated with some parameters such as treatment. Thus, more detailed investigations about the risk for primary lung cancer in patients with different types of FHRCs should be further conducted, which would contribute to the clinical management of the risk of subsequent primary lung cancer among FHRC patients.

In the past decade, the incidence rate of lung cancer in women has increased significantly, which may be related to secondhand smoke, cooking oil fumes, wood combustion, and air pollution.[76–79] However, these risk factors cannot fully explain the high incidence of lung cancer because a considerable proportion of patients are not exposed to these factors. Therefore, it is necessary to identify more fundamental factors associated with FHRC patients. Some scholars have indicated that a great number of female lung cancer patients have sex hormone-dependent lung cancer, which is closely associated with some parameters, such as age and adenocarcinoma.[80–82] It has been reported that estrogen receptors, especially estrogen receptor beta (ERβ), are expressed in pulmonary tissues and overexpressed in tumor tissues in some female lung adenocarcinoma patients,[83,84] which is related to the elevated expression level of estrogen.[85] To date, several pathways have been shown to be closely associated with the carcinogenic role of estrogen in women. First, metabolites of estrogen can produce reactive oxygen species (ROSs), which cause oxidative damage to deoxyribonucleic acid (DNA), leading to mutations.[84] Second, the estrogen/estrogen receptor (ER) complex can promote the proliferation and cell cycle progression of lung cancer cells by activating some estrogen expression-dependent genes, such as the cyclin D, c-Myc, and inhibitor of differentiation (ID) genes.[6,10] Third, estrogen has been demonstrated to play a role

in stimulating tumor growth and sustaining tumor cell proliferation by activating several pathways, such as the cAMP and PI3K pathways.[6,7] Fourth, previous studies have indicated that estrogen stimulates the expression of C-X-C chemokine receptor type 4 (CXCR4) and activation of the C-X-C motif chemokine ligand 12 (CXCL12)/CXCR4 pathway in a time- and dose-dependent manner, which affects cell proliferation, migration, survival, apoptosis resistance, and the tumor microenvironment.[86,87] Fifth, as mentioned above, estrogen plays a role in promoting angiogenesis through the VEGF-A/VEGFR-2 pathway, contributing to tumor growth.[10] Sixth, it is well known that the epidermal growth factor receptor (EGFR) pathway is the most important signaling pathway of lung adenocarcinoma. Estrogen can activate the EGFR pathway, which promotes cell proliferation, angiogenesis, migration, and metastasis.[9] In addition, ERβ is reported to be significantly related to *EGFR* mutations.[8]

Breast, endometrial, cervical, and ovarian cancers are the most common tumors in women, and it has been widely verified that breast, endometrial, and ovarian cancers are estrogen-related tumors and that high levels of estrogen expression are usually observed in most cases.[88,89] The occurrence of cervical carcinoma is strongly associated with early marriage, childbearing, sexual life, times of pregnancy, and human papillomavirus (HPV) infection.[90] However, recent evidence indicates that high levels of estrogen increase susceptibility to HPV infection, especially high-risk HPV-16 infection.[91] Moreover, a synergistic effect between high estrogen levels and HPV infection promotes the occurrence of cervical lesions, which in turn leads to cervical carcinoma.[91] Thus, it is objective and appropriate to define these four cancers as FHRC.

Our results indicated an obvious trend of increasing lung cancer risk over time among overall FHRC patients, breast cancer patients, and ovarian cancer patients. We deem that systemic chemotherapy is the main reason for this interesting phenomenon. Most breast and ovarian cancer patients receive neoadjuvant chemotherapy or adjuvant chemotherapy. Combining with previous relevant studies, chemotherapy is believed to play a role in increasing the risk of secondary tumors when patients are observed long enough,[92,93] although it may show a protective effect in the short term (e.g., less than five years).[13] The main reasons for the increased risk of secondary tumors from chemotherapy include the increased permeability and number of blood vessels in the tumor metastasis microenvironment.[94] In our meta-analysis, FHRC patients receiving chemotherapy did show a higher risk of subsequent primary lung cancer than the general population, but only three included studies explored the relationship between chemotherapy and the risk of secondary lung cancer. Therefore, more high-quality studies are needed to verify the above findings. On the other hand, an opposite trend was observed in endometrial cancer patients. One of the potential reasons is the later age of onset, namely, more than three-quarters of patients are older than 50 years and postmenopausal.[95] In other words, the estrogen level in most endometrial cancer patients with longer survival time is relatively low, which is consistent with the results of this meta-analysis. For radiotherapy, the risk for subsequent lung cancer could be affected by radiotherapy only in breast cancer patients due to the adjacent sites. In the study we published in 2021, radiotherapy was demonstrated to be one of the risk factors for developing lung cancer among breast cancer patients (relative risk [RR] = 1.40, P <0.001).[13] Overall, younger FHRC patients are more likely to develop subsequent primary lung cancer than the general population compared to older patients according to our results. We hypothesize that this phenomenon is mainly associated with the longer follow-up period of younger patients and the higher incidence of lung cancer in people over the age of 50 years.[96]

There are several limitations in this meta-analysis. First, all included studies were retrospective, which might cause some bias. Second, significant heterogeneity was detected in our meta-analysis, and we were unable to identify the sources of heterogeneity based on available data. Third, more specific subgroup analyses stratified by other parameters, such as smoking, family history, and periods between primary and subsequent primary cancers (asynchronous *vs*. synchronous), were unable to be conducted. Fourth, in this type of study, we were unable to better identify and correct confounding factors due to the lack of original data. Fifth, several studies only reported the sample size of the total study population and did not provide the specific number of cases for each FHRC.[21,27,28,42,55] Six, the sensitivity analysis for the endometrial cancer manifested that the relationship between endometrial cancer and increased risk of subsequent primary lung cancer is not absolutely reliable, and further research is needed to verify our findings. Seven, we conducted the subgroup analysis based on the follow-up period (<5 years, ≥5 years, ≥10 years, etc). However, due to the limited data, we were unable to conduct more specific analysis based on subgroups such as <5 years, 5–10 years, 11–20 years and 21–30 years.

In conclusion, FHRC patients are more likely to develop lung cancer than the general population based on four million cases. In addition, the increased risk for subsequent primary lung cancer is more obvious with a longer survival time and is observed in all types of hormone-related cancer. However, more detailed analyses focusing on each group of FHRC patients are still needed in future studies.

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Conflicts of interest

None.

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