The Association between Smoking and Mortality in Women with Breast Cancer: A Real-World Database Analysis

Yi-Chen Lai 1,†, Yu-Han Chen 2,†, Yu-Cih Wu 3, Fu-Wen Liang 4,5, Jhi-Joung Wang 3, Sher-Wei Lim 6,7,* and Chung-Han Ho 3,8,9,†

Abstract: Smoking increases the cancer-specific and overall mortality risk in women with breast cancer (BC). However, the effect of smoking cessation remains controversial, and detailed research is lacking in Asia. We aimed to investigate the association between smoking status and mortality risk in women diagnosed with breast cancer between 2011 and 2017 using a real-world population database. Women with breast cancer with a history of smoking had a 1.25-fold higher (95% C.I.: 1.08–1.45; p = 0.0022) risk of overall mortality and a 1.22-fold higher (95% C.I.: 1.04–1.44; p = 0.0407) risk of overall mortality compared with ever smokers. It was shown that a current smoking status is significantly associated with an increase in overall and cancer-specific mortality risk in women with breast cancer. Among women diagnosed with breast cancer, those who quit smoking had a lower mortality risk than current smokers. Our results underscore the importance of smoking cessation for women with BC.

Simple Summary: The association between smoking status and breast cancer mortality in Asian populations has not been extensively studied. In this study, we aimed to investigate the association between smoking status and mortality risk in women diagnosed with breast cancer between 2011 and 2017 using a real-world population database. Women with breast cancer with a history of smoking had a 1.25-fold higher (95% C.I.: 1.08–1.45; p = 0.0022) risk of overall mortality and a 1.22-fold higher (95% C.I.: 1.04–1.44; p = 0.0407) risk of overall mortality compared with ever smokers. It was shown that a current smoking status is significantly associated with an increase in overall and cancer-specific mortality risk in women with breast cancer. Among women diagnosed with breast cancer, those who quit smoking had a lower mortality risk than current smokers. Our results underscore the importance of smoking cessation for women with BC.
mortality risk in women with BC. Quitting smoking could reduce one’s mortality risk. Our results underscore the importance of smoking cessation for women with BC.

**Keywords:** breast cancer; smoking; mortality; real-world database

### 1. Introduction

In 2020, female breast cancer was the most commonly diagnosed cancer and caused 684,996 deaths worldwide [1]. Its incidence rate was also the highest in the female population in Taiwan and far exceeded that of other types of cancer [2]. The prognosis of breast cancer patients is not only dependent on the characteristics of the tumor [3], but it is also closely related to several potentially modifiable lifestyle factors, such as smoking status, alcohol intake, weight control, and physical activity [4–6].

Smoking is a well-known all-cause mortality risk in the general population, with causes including vascular diseases, respiratory diseases, and cancers [7,8], and this risk decreases as the number of years after the cessation of smoking increases [9,10]. Smoking has stronger health effects in women than in men regarding the risk of several diseases, such as coronary heart disease, COPD (chronic obstructive pulmonary disease), and specific cancers such as colorectal cancer, bladder cancer, and breast cancer [11,12]. The association between smoking status and the risk of mortality in women with breast cancer has previously been investigated in several studies, but it has not been extensively explored in Asian countries.

Among women with breast cancer, according to the previous literature, current smokers have approximately 1.5 to 3 times higher all-cause mortality rates and 1.2 to 2 times higher cancer-specific mortality rates when compared to never smokers, and the risk of mortality is positively related to the intensity and duration of smoking [13–17]. Several studies also revealed that smoking status was not significantly associated with mortality risk among women with BC, but such literature is relatively rare [18,19]. Tobacco smoke contains hundreds of carcinogenic molecules, and it has been shown to facilitate angiogenesis, tumor growth, and epithelial–mesenchymal transition; it is also associated with axillary lymph node and pulmonary metastasis [20–22]. Fortunately, two recent meta-analyses revealed that the cessation of smoking dramatically decreases the risk of cancer-specific mortality to a level near that of never smokers in women with breast cancer, and cessation also reduces the risk of all-cause mortality in these patients [4,23]. However, the literature also revealed that women with breast cancer do not significantly alter their smoking habits after their diagnosis compared to cancer-free women, and the quitting rate was also shown to be lower than that in patients with other cancer types, such as lung cancer and colorectal cancer [4,24,25].

As an important modifiable factor associated with the prognosis of women with breast cancer, smoking habits must be reduced to improve the quality of care and the survival rate of these patients. A detailed characterization of the relationship between smoking and prognosis is vital to encourage smoking cessation when providing education and lifestyle advice to specific groups of women with breast cancer. With this goal in mind, we conducted a population-based, retrospective cohort study to analyze the effect of smoking on mortality risk in women with breast cancer of different ages and with different disease stages, comorbidities, BMIs (body mass indexes), treatment courses, and intensities and durations of smoking habits.

### 2. Materials and Methods

#### 2.1. Data Source

The Taiwan Cancer Registry (TCR) was used to identify women with breast cancer. The TCR was established in 1979 to gather information regarding individual demographics, cancer stages, primary cancer sites, tumor histology, and treatment types in patients with cancer to understand the incidence and mortality rates of cancer in Taiwan. Within the
registry, the definition of cancer types is based on the International Classification of Diseases for Oncology, third edition (ICD-O-3). The TCR has been used in its short-form and long-form format in different periods to examine different major cancers.

The disease comorbidities of women with breast cancer were collected from the National Health Insurance Research database (NHIRD). The NHIRD contains data from Taiwan’s single-payer population insurance system, in which more than 99% of Taiwan’s 23 million citizens are registered. The diagnosis codes in the NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In addition, the death records are based on the database of death registration for the population of Taiwan.

The above databases are managed by the Health and Welfare Data Science Center (HWDC) of the Ministry of Health and Welfare. Only researchers can apply to use these databases for research purposes. After verification, the HWDC provides the relevant databases and presents de-identified forms to researchers. The HWDC released the above database to us in a de-identified and anonymized format, and we only used the database provided by the HWDC [26]. This study was conducted in compliance with the Declaration of Helsinki of 1964 and has been approved by the Ethics Committee of the Institutional Review Board of Chi-Mei Hospital (IRB:10912-E02). The requirement for informed consent was waived by the Research Ethics Committee of Chi Mei Hospital.

2.2. Study Population

Women with new-onset breast cancer (ICD-O-3: C50) from January 2011 to December 2017 were enrolled in this study because TCR started to record the smoking information in 2011. Women with a history of breast cancer before 2011 were excluded. Patients with uncompleted records regarding all of the variables examined were excluded. All of the study subjects were divided into a group of women with breast cancer with a smoking history (current and former smokers) and a group of those without a smoking history (non-smokers). The group with a smoking history included current smokers and former smokers in order to consider the effect of nicotine. According to the guidelines of the Taiwan Cancer Registry, on the date they were initially diagnosed with breast cancer, women were asked by a physician about their smoking status; the presence of smoking, the number of packs smoked per day, and smoking year were determined. Figure 1 illustrates the flowchart of subject selection in the study.

![Figure 1. Study selection flowchart.](image-url)
2.3. Outcome and Measurements

The primary outcome in this study was mortality, which was identified using Taiwan’s cause-of-death database. Overall mortality and cancer-specific mortality were both considered in this study to avoid bias when attributing the cause of death.

Considering that potential confounding factors may affect the mortality risk in women diagnosed with breast cancer, age, clinical stage, comorbidities, CCI score, treatment types, behavior, and BMI were measured in this study. In Taiwan, at the age of 45, women can receive free breast cancer screening [27]; therefore, all of the women in the study were classified into four age groups: <45 years, 45–54 years, 55–64 years, and ≥65 years. Comorbidities were defined using the ICD-9-CM or ICD-10-CM, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, renal disease, hypertension, hyperlipidemia, diabetes, and liver disease (Supplemental Table S1). The comorbidities were all presented as yes/no.

Charlson’s comorbidity index (CCI) score is a useful tool to predict mortality risk [28,29], and in this study, we divided the participants’ CCI scores into five groups: 0, 1, 2, 3, and ≥3. The comorbidities and CCI scores were recorded in patients who had at least three outpatient visits or one inpatient visit within one year before the date of the diagnosis of breast cancer to reduce the potential misclassification bias. The measurements regarding health behaviors included drinking alcohol, chewing betel nuts, and BMI. In addition, the treatment types, including operations, radiotherapy, and chemotherapy, were evaluated regarding their relationship with mortality.

2.4. Statistical Analysis

The differences in continuous variables and categorical variables between the women with breast cancer who smoked and those who did not smoke were evaluated using Student’s t-test and Pearson’s chi-square test, respectively. The Kaplan–Meier method was used to plot the trend of mortality that the follow up for all of the women started on the date of the diagnosis of breast cancer, and the log-rank test was used to compare the risk of mortality between the two groups. Cox proportional regression analysis was used to estimate the association of the risk of mortality with the hazard ratios (HRs) and 95% confidence intervals (CIs). According to the Schoenfeld residuals test, the assessment of proportional hazard assumption was approved. Multivariable Cox regression was used to present a full model which included smoking status, age, clinical stage, drinking, CCI score, BMI, comorbidities, and treatment types. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA). The statistical significance was set at a p-value < 0.05. The Kaplan–Meier curves were plotted using STATA (version 16; Stata Corp., College Station, TX, USA).

3. Results

In this study, 54,614 women with breast cancer were enrolled, including 1687 women who smoked and 52,927 who did not smoke. The baseline characteristics between smokers and non-smokers among women with breast cancer are presented in Table 1. The distributions of age, clinical stages, drinking alcohol, chewing betel nuts, CCI score, and BMI showed significant differences between women with breast cancer who smoked and those who did not.

Figure 2 illustrates the trends regarding overall mortality and cancer-specific mortality development between smokers and non-smokers with breast cancer (log-rank test $p = 0.1552$ for overall and $p = 0.0473$ for cancer-specific mortality).

The overall mortality risk and cancer-specific mortality risk for smokers and non-smokers in women with breast cancer among all of the patients and stratified characteristics are presented in Table 2. After adjusting for age, clinical stage, drinking alcohol, chewing betel nuts, CCI score, BMI, comorbidities, and treatment types, smokers had a 1.25-fold higher (95% C.I.: 1.08–1.45; $p = 0.0022$) risk of overall mortality and a 1.22-fold higher (95% C.I.: 1.04–1.44; $p = 0.0168$) risk of cancer-specific mortality compared with non-smokers.
The stratified analysis of different age groups indicated significant overall and cancer-specific mortality risks in women older than 55, and it was shown that smokers had higher mortality risks than non-smokers. It was also shown that women with breast cancer in late clinical stages (III and IV) who also smoked had significant overall mortality risks compared with non-smokers, but there was only borderline significance regarding the cancer-specific mortality risk. In the current study, we also found that smokers had a 1.43-fold higher risk (95% CI: 1.07–1.92; \( p = 0.0164 \)) of overall mortality than non-smokers in women with breast cancer who drank alcohol. Regarding the CCI score, it was shown that smokers with CCI = 0 had significantly higher overall mortality risks (HR: 1.20; 95% CI: 1.01–1.43; \( p = 0.0408 \)) than non-smokers, but the same estimation was not shown regarding cancer-specific mortality. Smokers with CCI > 3 and those that received chemotherapy also showed significantly higher overall and cancer-specific mortality risks than non-smokers.

Table 1. Baseline characteristics between smokers and non-smokers among women with breast cancer.

| Age group, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|------------------|--------------------------|-------------------|--------------|
| <45              | 9681 (18.29)             | 509 (30.17)       | <0.0001      |
| 45–54            | 16,705 (31.56)           | 676 (40.07)       |              |
| 55–64            | 15,118 (28.56)           | 335 (19.86)       |              |
| >=65             | 11,423 (21.58)           | 167 (9.90)        |              |

| Clinical Stage, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|----------------------|--------------------------|-------------------|--------------|
| I                    | 19,578 (36.99)           | 551 (32.66)       | 0.0042       |
| II                   | 24,368 (46.04)           | 827 (49.02)       |              |
| III                  | 5195 (9.82)              | 178 (10.55)       |              |
| IV                   | 3786 (7.15)              | 131 (7.77)        |              |

| Drinking Alcohol, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|-------------------------|--------------------------|-------------------|--------------|
|                         | 1770 (3.34)              | 553 (32.78)       | <0.0001      |

| Chewing Betel Nuts, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|---------------------------|--------------------------|-------------------|--------------|
|                          | 152 (0.29)               | 90 (5.33)         | <0.0001      |

| CCI, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|------------|--------------------------|-------------------|--------------|
| 0          | 38,854 (73.41)           | 1317 (78.07)      | 0.0004       |
| 1          | 7401 (13.98)             | 203 (12.03)       |              |
| 2          | 3628 (6.85)              | 92 (5.45)         |              |
| 3          | 1536 (2.90)              | 32 (1.90)         |              |
| >3         | 1508 (2.85)              | 43 (2.55)         |              |

| BMI, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|------------|--------------------------|-------------------|--------------|
| <18.5      | 2291 (4.33)              | 130 (7.71)        | <0.0001      |
| 18.5–25    | 30,228 (57.11)           | 1021 (60.52)      |              |
| 25–30      | 15,162 (28.65)           | 384 (22.76)       |              |
| 30–35      | 4176 (7.89)              | 124 (7.35)        |              |
| >35        | 1070 (2.02)              | 28 (1.66)         |              |

| Death, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|--------------|--------------------------|-------------------|--------------|
|              | 6069 (11.47)             | 211 (12.51)       | 0.1872       |

| Death within 5 years, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|-----------------------------|--------------------------|-------------------|--------------|
|                            | 5470 (10.35)             | 191 (11.32)       | 0.1905       |

| Death due to breast cancer, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|----------------------------------|--------------------------|-------------------|--------------|
|                                  | 4536 (8.57)              | 167 (9.90)        | 0.0554       |

| Comorbidity, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|--------------------|--------------------------|-------------------|--------------|
| Myocardial infarction | 97 (0.18)                | 5 (0.30)          | 0.2488       |
| Congestive heart failure | 525 (0.99)              | 12 (0.71)         | 0.2502       |
| Peripheral vascular disease | 186 (0.35)             | 8 (0.47)          | 0.4040       |
| Cerebrovascular disease | 1486 (2.81)             | 36 (2.13)         | 0.0979       |
| Dementia            | 476 (0.90)               | 7 (0.41)          | 0.0364       |
| Chronic pulmonary disease | 1804 (3.41)            | 78 (4.62)         | 0.0071       |
| Renal disease       | 1136 (2.15)              | 23 (1.36)         | 0.0280       |
| Hypertension        | 11,137 (21.04)           | 252 (14.94)       | <0.0001      |
| Hyperlipidemia      | 8131 (15.36)             | 184 (10.91)       | <0.0001      |
| Diabetes            | 6068 (11.46)             | 141 (8.36)        | <0.0001      |
| Liver disease       | 1368 (2.58)              | 42 (2.49)         | 0.8085       |

| Treatment, n (%) | Non-Smokers (N = 52,927) | Smokers (N = 1687) | \( p \)-Value |
|------------------|--------------------------|-------------------|--------------|
| Operation        | 49,499 (93.52)           | 1574 (93.30)      | 0.7161       |
| Radiotherapy     | 29,588 (55.90)           | 1007 (56.69)      | 0.0020       |
| Chemotherapy     | 35,136 (66.39)           | 1240 (73.50)      | <0.0001      |
The comparison between ever smokers and current smokers regarding overall and cancer-specific mortality risks is shown in Table 3. After adjustments of the selected risk factors, current smokers had a 1.57-fold higher risk (95% CI: 1.03–2.44; \( p = 0.0407 \)) of overall mortality compared with ever smokers. Additionally, the stratified analysis of mortality risk between women who quit smoking and those who did not smoke is presented as Table 4. Current smokers who drank alcohol (HR: 3.08; 95% CI: 1.38–6.85; \( p = 0.0058 \)), had a CCI = 0 (HR: 2.01; 95% CI: 1.12–3.61; \( p = 0.0196 \)), and received radiotherapy (HR: 3.05; 95% CI: 1.39–6.69; \( p = 0.0053 \)) showed a significantly higher overall mortality risk compared with former smokers. In terms of cancer-specific mortality risk, the estimated mortality risk was as similar to the overall mortality risk. However, women aged 45–54 (HR: 3.67; 95% CI: 1.18–11.43; \( p = 0.0246 \)) and 55–64 (HR: 10.66; 95% CI: 1.63–69.48; \( p = 0.0134 \)) who currently smoked presented higher risks than women who quit smoking.
Table 2. The risk of mortality between smokers and non-smokers among women with breast cancer stratified by characteristics.

| Smokers vs. Non-Smokers | Overall Mortality | Cancer-Specific Mortality |
|-------------------------|-------------------|--------------------------|
|                         | Patient, N        | Death, N (%)             | Crude HR (95% CI) * | AHR (95% CI) * | p-Value | Death, N (%) | Crude HR (95% CI) | AHR (95% CI) * | p-Value |
| Overall                 | 1687              | 211 (12.51)              | 1.10 (0.96–1.27)     | 1.25 (1.08–1.45) | 0.0022 | 167 (9.9)    | 1.17 (1.00–1.36)  | 1.22 (1.04–1.44) | 0.0168 |
| Stratified              |                   |                           |                       |                 |         |              |                          |                 |        |
| Age group               |                   |                           |                       |                 |         |              |                          |                 |        |
| <45                     | 509               | 45 (8.84)                 | 1.16 (0.86–1.57)      | 1.17 (0.84–1.62) | 0.3858 | 40 (7.86)    | 1.13 (0.82–1.56)  | 1.14 (0.81–1.62) | 0.4476 |
| 45–54                   | 676               | 70 (10.36)                | 1.16 (0.91–1.47)      | 1.19 (0.92–1.54) | 0.1851 | 53 (7.84)    | 1.00 (0.76–1.32)  | 1.00 (0.75–1.34) | 0.9838 |
| 55–64                   | 335               | 44 (13.13)                | 1.31 (0.97–1.77)      | 1.34 (0.98–1.83) | 0.0687 | 38 (11.34)   | 1.47 (1.06–2.03)  | 1.49 (1.06–2.09) | 0.0220 |
| >=65                    | 167               | 52 (31.14)                | 1.75 (1.33–2.30) *    | 1.46 (1.10–1.95) | 0.0093 | 36 (21.56)   | 2.05 (1.47–2.85) **| 1.54 (1.09–2.18) | 0.0142 |
| Clinical Stage          |                   |                           |                       |                 |         |              |                          |                 |        |
| I                       | 551               | 17 (3.09)                 | 1.08 (0.67–1.75)      | 1.56 (0.95–2.57) | 0.0791 | 9 (1.63)     | 1.45 (0.74–2.81)  | 1.65 (0.82–3.29) | 0.1577 |
| II                      | 827               | 66 (7.98)                 | 0.92 (0.72–1.17)      | 1.07 (0.83–1.38) | 0.6166 | 45 (5.44)    | 0.98 (0.73–1.32)  | 0.99 (0.73–1.36) | 0.9596 |
| III                     | 178               | 48 (26.97)                | 1.22 (0.91–1.62)      | 1.54 (1.12–2.10) | 0.0071 | 39 (21.91)   | 1.23 (0.89–1.69)  | 1.40 (0.99–1.99) | 0.0554 |
| IV                      | 131               | 80 (61.07)                | 1.14 (0.91–1.43)      | 1.27 (1.00–1.61) | 0.0486 | 74 (56.49)   | 1.16 (0.92–1.46)  | 1.26 (0.99–1.62) | 0.0630 |
| Drinking Alcohol        | 553               | 72 (13.02)                | 1.38 (1.05–1.81) *    | 1.43 (1.07–1.92) | 0.0164 | 58 (10.49)   | 1.32 (0.97–1.78)  | 1.34 (0.97–1.85) | 0.0808 |
| Chewing Betel Nuts      | 90                | 21 (23.33)                | 1.72 (0.94–3.16)      | 1.25 (0.56–2.80) | 0.5832 | 17 (18.89)   | 2.11 (1.04–4.28)  | 1.30 (0.33–5.06) | 0.7095 |
| CCI                     |                   |                           |                       |                 |         |              |                          |                 |        |
| 0                       | 1317              | 144 (10.93)               | 1.18 (1.00–1.40) *    | 1.20 (1.01–1.43) | 0.0408 | 118 (8.96)   | 1.14 (0.95–1.38)  | 1.11 (0.91–1.35) | 0.3052 |
| 1                       | 203               | 19 (9.36)                 | 0.78 (0.49–1.22)      | 0.99 (0.61–1.59) | 0.9626 | 17 (8.37)    | 0.98 (0.61–1.59)  | 1.13 (0.68–1.89) | 0.6370 |
| 2                       | 92                | 17 (18.48)                | 1.11 (0.68–1.79)      | 1.56 (0.94–2.69) | 0.0843 | 14 (15.22)   | 1.54 (0.90–2.63)  | 2.18 (1.23–3.89) | 0.0081 |
| 3                       | 32                | 9 (28.13)                 | 1.39 (0.72–2.70)      | 1.28 (0.63–2.62) | 0.4947 | 5 (15.63)    | 1.41 (0.58–3.43)  | 0.77 (0.29–2.09) | 0.6117 |
| >=3                     | 43                | 22 (51.16)                | 1.38 (0.90–2.11)      | 2.02 (1.28–3.19) | 0.0025 | 15 (30.23)   | 1.74 (1.00–3.03)  | 2.69 (1.48–4.89) | 0.0012 |
| Treatment               |                   |                           |                       |                 |         |              |                          |                 |        |
| Operation               | 1574              | 141 (8.96)                | 1.10 (0.93–1.30)      | 1.19 (1.00–1.42) | 0.0558 | 106 (6.73)   | 1.19 (0.98–1.44)  | 1.12 (0.92–1.38) | 0.2627 |
| Radiotherapy            | 1007              | 92 (9.14)                 | 1.12 (0.91–1.38)      | 1.28 (1.03–1.59) | 0.0286 | 71 (7.05)    | 1.07 (0.85–1.36)  | 1.18 (0.92–1.52) | 0.1857 |
| Chemotherapy            | 1240              | 173 (13.95)               | 1.21 (1.04–1.41) *    | 1.35 (1.15–1.59) | 0.0003 | 143 (11.53)  | 1.19 (1.01–1.41)  | 1.28 (1.07–1.53) | 0.0063 |

* p < 0.05, ** p < 0.0001. * Adjusted for age groups (<45, 45–54, 55–64, and >=65), clinical stage (I, II, III, and IV), drinking alcohol, chewing betel nuts, CCI groups (0, 1, 2, 3, and >=3), BMI groups (<18.5, 18.5–25, 25–30, 30–35, and >35), comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, renal disease, hypertension, hyperlipidemia, diabetes mellitus, and liver disease), and treatments (operation, radiotherapy, and chemotherapy).
Table 3. The risk of mortality between ever smokers and current smokers.

| Smokers | Yes | No  |
|--------|-----|-----|
| 0.5 pack/day | 828 | 95 (11.47) | Ref. |
| 1 pack/day | 734 | 95 (12.94) | 1.17 (0.88–1.55) |
| >1 pack/day | 125 | 21 (16.8) | 1.46 (0.91–2.34) |

| Age group | 0–10 | 11–20 | 21–30 | >30 |
|-----------|------|-------|-------|-----|
| Smokers   | 568  | 52 (9.15) | Ref. | Ref. |
| 45–54     | 676  | 70 (10.36) | 1.24 (0.85–1.80) | 0.2323 |
| 55–64     | 335  | 44 (13.13) | 1.67 (1.23–2.60) | 0.0023 |
| >65       | 167  | 52 (31.14) | 4.37 (2.93–6.62) | <0.0001 |

| Clinical stage | I | II | III | IV |
|----------------|---|----|-----|----|
| Smokers        | 551| 66 (7.98) | 2.48 (1.45–4.22) | <0.0009 |
|                | 827| 66 (7.98) | 2.48 (1.45–4.22) | <0.0009 |
|                | 178| 48 (26.97) | 1.77 (1.07–2.93) | 0.0261 |
|                | 131| 80 (61.07) | 2.82 (1.44–5.54) | 0.0026 |

| Drinking alcohol | Yes | No  |
|------------------|-----|-----|
| 553              | 72 (13.02) | 1.01 (0.76–1.35) |

| Chewing betel nuts | Yes | No  |
|--------------------|-----|-----|
| 90                 | 21 (23.33) | 2.01 (1.28–3.15) |

| CCI | 0 | 1 | 2 | 3 |
|-----|---|---|---|---|
| Smokers        | 1317| 144 (10.93) | Ref. | Ref. |
|                | 203 | 19 (9.36)   | Ref. | Ref. |
|                | 92  | 17 (18.48)  | N/A  | N/A  |

* Adjusted for smoking count (0.5, 1, and >1 pack/day), smoking year (0–10, 11–20, 20–30, and >30), age groups (<45, 45–54, 55–64, and ≥65), clinical stage (I, II, III, and IV), drinking alcohol, chewing betel nuts, CCI groups (0, 1, 2, 3, and ≥4), BMI groups (<18.5, 18.5–25, 25–30, 30–35, and ≥35), comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, renal disease, hypertension, hyperlipidemia, diabetes mellitus, and liver disease), and treatments (operation, radiotherapy, and chemotherapy).
Table 4. The stratified analysis of mortality risk between women who quit smoking and those who did not.

| Stratified | Overall Mortality | Cancer-Specific Mortality |
|------------|-------------------|---------------------------|
|            | AHR *(95%CI)      | p-Value                   | AHR *(95%CI)      | p-Value                   |
| Quit smoking, no vs. yes |                   |                           |                   |                           |
| Age group |                   |                           |                   |                           |
| <45       | 1.86 (0.61–5.68)  | 0.2788                    | 1.75 (0.58–5.32)  | 0.3249                    |
| 45–54     | 2.24 (0.90–5.39)  | 0.0850                    | 3.67 (1.18–11.43) | 0.0246                    |
| 55–64     | 4.10 (1.00–16.85) | 0.0508                    | 10.66 (1.63–69.48)| 0.0134                    |
| >=65      | 1.07 (0.42–2.72)  | 0.8831                    | 0.72 (0.24–2.13)  | 0.5530                    |
| Clinical Stage |                   |                           |                   |                           |
| Early stage | 1.33 (0.63–2.83)  | 0.4537                    | 1.76 (0.61–5.07)  | 0.2927                    |
| Last stage  | 1.74 (0.97–3.12)  | 0.0625                    | 1.51 (0.83–2.75)  | 0.1769                    |
| Drinking Alcohol | 3.08 (1.38–6.85)  | 0.0058                    | 3.93 (1.51–10.18) | 0.0049                    |
| CCI        |                   |                           |                   |                           |
| 0          | 2.01 (1.12–3.61)  | 0.0196                    | 2.21 (1.16–4.20)  | 0.0157                    |
| 1–2        | 0.99 (0.24–4.13)  | 0.9876                    | 1.21 (0.24–6.06)  | 0.8174                    |
| >=3        | 0.38 (0.06–2.57)  | 0.3240                    | N/A              | 0.9983                    |
| Treatment  |                   |                           |                   |                           |
| Operation  | 1.67 (0.91–3.04)  | 0.0971                    | 1.75 (0.85–3.62)  | 0.1281                    |
| Radiotherapy | 3.05 (1.39–6.69)  | 0.0053                    | 2.89 (1.19–7.02)  | 0.0193                    |
| Chemotherapy | 1.53 (0.93–2.54)  | 0.0953                    | 1.66 (0.96–2.88)  | 0.0726                    |

* Adjusted for smoking count (0.5, 1, and >1 pack/day), smoking year (0–10, 11–20, 20–30, and >30), age groups (<45, 45–54, 55–64, and >=65), clinical stage (I, II, III, and IV), drinking alcohol, chewing betel nuts, CCI groups (0, 1, 2, 3, and >3), BMI groups (<18.5, 18.5–25, 25–30, 30–35, and >=35), comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, renal disease, hypertension, hyperlipidemia, diabetes mellitus, and liver disease), and treatments (operation, radiotherapy, and chemotherapy).

4. Discussion

This large, real-world database study investigated the association between cigarette smoking and mortality risk in women with breast cancer in Asia. Cigarette smoke contains at least 69 known carcinogens, and some of them have been shown to be capable of reaching human breast tissue [30,31]. p53 gene mutations and smoking-related DNA adducts found in smokers’ breast tissue explained the positive association between cigarette smoking and the risk of breast cancer [32,33]. Furthermore, the literature also demonstrated that cigarette smoking increases the motility and invasiveness of breast epithelial cells, and smoking is associated with an increased risk of pulmonary metastasis and lymph node metastasis among women with breast cancer [20,22]. In line with previous studies, which were mainly conducted in Western countries, our results revealed that, in women diagnosed with breast cancer, current smokers have a significant increased overall mortality and cancer-specific mortality risk when compared to never smokers, with a mild and more obvious effect on the overall mortality than the cancer-specific mortality risk [4,15,17,23,34]. The only research in Asia that analyzed the association between smoking status and mortality risk in women with breast cancer was conducted in Japan, which included 880 women and revealed that current smokers displayed no significant increase in all-cause death and breast cancer-specific death rates among all of the women [35]; however, their result should be interpreted with caution due to the relatively small sample size. No increases in overall mortality and cancer-specific mortality risks were found in the former smokers in the present study, which implies that better survival outcomes can be achieved after women with breast cancer quit smoking. The majority of the previous literature demonstrated that a former smoking status increases all-cause mortality but not breast-cancer-specific mortality risk [4,15,23]. The effect of a former smoking status on all-cause mortality risk may be associated with the duration and intensity of smoking. A population-based, prospective, observational study conducted by Passarelli et al. revealed that former smokers were
only associated with significant increases in all-cause mortality risk when the smoking duration ≥30 years or amount ≥30 pack-years [34].

4.1. Effect Modification by Clinical Stage, Treatment Strategy, and Comorbidities

In our study, the impact of smoking cessation on the risk of mortality was shown to be more prominent in women in the later stages of breast cancer. This result is slightly different from previous research. A retrospective cohort study in the US showed that smoking cessation was associated with improved survival status amongst breast cancer survivors across all stages, and the strength of this relationship was stronger in stage 1 (RR = 2.77, p = 0.34) than in stage 3 (RR = 1.35, p = 0.42) breast cancer [36]. Two prospective cohort studies also revealed a more prominent difference between current and former smokers in patients with local disease than in regional/distant disease [37,38]. The high 5-year survival rate of women with early-stage breast cancer in Taiwan (100% in stage 0 and stage 1 and 94% in stage 2) [39] may mean that the effect of smoking cessation on the survival rate in patients with stage 0–2 cancer appeared to be less significant in our cohort within the study period, leading to differences in the results.

The increases in mortality risk caused by smoking and the significantly lower overall and breast cancer-specific mortality risk found in former smokers than in current smokers were similar among patients receiving various types of breast cancer therapy in this study, which implies that the potential benefits of the cessation of smoking on survival outcomes do not vary with treatment options. It has been well documented that smoking during cancer treatment was associated with the development of secondary malignancy [40] and post-treatment complications [41]. A population-based nested case–control study conducted by Kaufman et al. showed that post-mastectomy radiotherapy (PMRT) sharply increased the risk of second primary lung cancer among ever smokers (adjusted OR = 18.9, 95% CI 7.9–45.4); however, information regarding smoking status was not documented in this study due to serious bias, and as a result, the difference between ex-smokers and current smokers was not compared [42]. A systemic review performed by Wong reported significant differences in multiple outcomes related to adjuvant breast cancer radiation treatment between smokers and non-smokers, including 41.7% of secondary carcinoma, 71.4% of reconstruction outcomes, and 33% of mortality outcomes [43]. Cigarette smoke has been well documented to impair the efficacy of chemotherapy [40,44], affect the liver metabolism of cytotoxic agents, and therefore increase the complication rates of chemotherapy [45]. The literature also revealed that smoking is associated with higher rates of overall and infectious post-operative complications, reconstructive failure, and flap necrosis [46], and these complication rates could be significantly decreased by the cessation of smoking, which was reported in a retrospective cohort study conducted in the US [47]. The results of this study supported these studies and further emphasized the benefit and importance of quitting smoking.

4.2. Effect Modification by Age, Alcohol Consumption, and the Duration and Intensity of Smoking

In this study, it was shown that a much higher percentage of smokers drink alcohol compared with non-smokers. A stronger association between smoking and mortality in alcohol consumers was observed in our results. A prospective cohort study conducted in Canada also revealed a more significant increased risk of breast-cancer-specific mortality associated with current smokers in long-term alcohol consumers (HR = 2.91 for moderate/high alcohol consumption; HR = 1.36 for None/Low) [48]. A plausible explanation for this is that the synergistic effects of cigarette smoking and alcohol consumption increase the level of estradiol, which regulates the expression of insulin-like growth factor-I (IGF-I) and stimulates the proliferation of mammary cells [49,50]. The overall and cancer-specific mortality risks for the former smokers were significantly lower than those of the current smokers who were alcohol consumers, which may imply that the cessation of smoking may be strongly associated with an improvement in survival prognosis in this subgroup. This
may also explain why our results showed that the death rate for the former smokers was significantly lower than that for the current smokers who were alcohol consumers.

The duration and intensity of cigarette smoking were positively associated with the risk of death in our study. A dose–response relationship was also found in many previous studies. Boone et al. demonstrated that the all-cause mortality risk was significantly higher for women who smoked ≥20 years (HR = 1.47) or ≥35 pack-years (HR = 1.82) in the US [48]. Bérubé et al. reported that women who smoked >30 pack-years had significantly higher breast-cancer-specific mortality (HR = 1.52) and all-cause mortality (HR = 1.83) risks in Canada [13], and Kakugawa et al. found that a duration of smoking >21.5 years was associated with significantly higher all-cause (HR = 3.09) and breast cancer-specific death rates (HR = 3.35) among premenopausal women in Japan [35]. The more significant increase in overall mortality and cancer-specific mortality risks related to smoking in patients older than 65 in this study may be related to the possibly longer duration of smoking habits in these patients. In addition, smoking duration and age showed a positive correlation, and this may explain why the effect was less significant among women aged <45 years.

The main strengths of this study include the large sample size contributed by Taiwan’s NHIRD, as well as the strong medical records regarding smoking habits and statuses retrieved from the population cancer registry database, instead of a single questionnaire or brief interview, which carry a substantial risk of underreporting [4,6,35]. As the first population-based study that investigated the association between mortality risk and smoking habits in women with breast cancer in Asia, our study provides important information regarding education and advice in terms of lifestyle adjustment in this patient group. However, there are several limitations to our study. First, the smoking statuses of current, former, and never smokers were determined using the patients’ statuses on the date of their breast cancer diagnosis, but information regarding the specific date of smoking cessation before diagnosis, the time of quitting, and whether smoking was quit after the diagnosis was not obtained from the medical records. This would have had an impact on our interpretation of the results. Second, information regarding passive smoking exposure could not be retrieved from the database, and the effect of passive smoking on breast cancer mortality risk remains controversial according to the previous literature [48,51,52]. Third, information regarding patients’ adherence to breast cancer treatment was not known, as we only obtained binary yes/no information concerning this aspect. Fourth, the HER2/estrogen/progesterone receptor status of the breast cancer patients was not retrieved from the NHIRD database for further adjustment and analysis, and these characteristics may have had confounding effects to the result. Fifth, due to the influence of traditional Taiwanese culture, the smoking rate of Taiwanese women is much lower than that of men [53], which means that the proportion of smokers in the present study was relatively low (2.9%), further limiting the generalizability of our results. However, according to the Taiwan Health and Welfare report of 2020, the smoking rate of adult women over 18 years old in Taiwan was 2.3–4.3% between 2011 and 2017, which was compatible with our result [39]. Last, similar to the issue regarding smoking status, we only measured the confounding factors on the date of breast cancer diagnosis, and these factors may have changed during the period following a patient’s diagnosis, which may have further affected the survival outcomes of the patients.

5. Conclusions

We found that ever smokers have a higher risk of overall and breast cancer-specific mortality than never smokers, and former smokers have lower risks of both compared to current smokers. Although the degrees of the benefits on different subgroups vary, there was no disagreement regarding these trends. Our study emphasized the importance of the cessation of smoking in women diagnosed with breast cancer and provided important information for clinicians when giving advice regarding lifestyle adjustment.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14194565/s1, Table S1: ICD-9 and ICD-10 Codes for Comorbidities.
Author Contributions: Conceptualization, Y.-C.L., Y.-H.C. and C.-H.H.; methodology, Y.-C.L., Y.-H.C. and C.-H.H.; validation, F.-W.L., S.-W.L. and C.-H.H.; formal analysis, Y.-C.W. and C.-H.H.; writing—original draft preparation, Y.-C.L., Y.-H.C. and C.-H.H.; writing—review and editing, F.-W.L., S.-W.L. and C.-H.H.; visualization, Y.-C.W.; supervision, J.-J.W.; funding acquisition, J.-J.W., S.-W.L. and C.-H.H. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Ministry of Health and Welfare, Taiwan, using health and welfare surcharge of tobacco products, grant number MOHW110-TDU-B-212-144020; Chi Mei Medical Center, grant number CMFHR11014; and Chi Mei Medical Center, Chiali, grant number CCFHR11005.

Institutional Review Board Statement: This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of Chi Mei Hospital (IRB no. 10912-E02).

Informed Consent Statement: Patient consent was waived due to the non-identification of patient data.

Data Availability Statement: The data sources are the Taiwan Nation Health Insurance Database and Taiwan Cancer Registry. The data are available with permission from the Taiwan Health and Welfare Data Science Center (https://dep.mohw.gov.tw/DOS/wp-2497-113.html, accessed on 19 June 2022). Restrictions apply to the availability of these data, which were used under license for this study.

Acknowledgments: We are grateful to the Health Data Science Center, National Cheng Kung University Hospital for providing administrative and technical support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]

2. Ministry of Health and Welfare. Taiwan Dementia Policy: A Framework for Prevention and Care; Ministry of Health and Welfare: Taipei, Taiwan, 2020.

3. Clarke, M.; Collins, R.; Darby, S.; Davies, C.; Elphinstone, P.; Evans, V.; Godwin, J.; Gray, R.; Hicks, C.; James, S.; et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005, 366, 2087–2106. [CrossRef] [PubMed]

4. Sollie, M.; Bille, C. Smoking and mortality in women diagnosed with breast cancer–a systematic review with meta-analysis based on 400,944 breast cancer cases. Gland Surg. 2017, 6, 383–393. [CrossRef] [PubMed]

5. Hamer, J.; Warner, E. Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. Cmaj 2017, 189, E268–E274. [CrossRef] [PubMed]

6. Tominaga, K.; Andow, J.; Koyama, Y.; Numao, S.; Kurokawa, E.; Ojima, M.; Nagai, M. Family environment, hobbies and habits as psychosocial predictors of survival for surgically treated patients with breast cancer. Jpn. J. Clin. Oncol. 1998, 28, 36–41. [CrossRef] [PubMed]

7. Jacobs, D.R., Jr.; Adachi, H.; Mulder, I.; Kromhout, D.; Menotti, A.; Nissinen, A.; Blackburn, H. Cigarette smoking and mortality risk: Twenty-five-year follow-up of the Seven Countries Study. Arch. Intern. Med. 1999, 159, 733–740. [CrossRef]

8. Prescott, E.; Osler, M.; Andersen, P.K.; Hein, H.O.; Borch-Johnsen, K.; Lange, P.; Schnohr, P.; Vestbo, J. Mortality in women and men in relation to smoking. Int. J. Epidemiol. 1998, 27, 27–32. [CrossRef]

9. Carter, B.D.; Abnet, C.C.; Feskanich, D.; Freedman, N.D.; Hartge, P.; Lewis, C.E.; Ockene, J.K.; Prentice, R.L.; Speizer, F.E.; Thun, M.J.; et al. Smoking and mortality—beyond established causes. N. Engl. J. Med. 2015, 372, 631–640. [CrossRef]

10. Banks, E.; Joshy, G.; Weber, M.F.; Liu, B.; Grenfell, R.; Egger, S.; Paige, E.; Lopez, A.D.; Sitas, F.; Beral, V. Tobacco smoking and all-cause mortality in a large Australian cohort study: Findings from a mature epidemic with current low smoking prevalence. BMC Med. 2015, 13, 38. [CrossRef]

11. Allen, A.M.; Oncken, C.; Hatsukami, D. Women and Smoking: The Effect of Gender on the Epidemiology, Health Effects, and Cessation of Smoking. Curr. Addict. Rep. 2014, 1, 53–60. [CrossRef]

12. Sørheim, I.C.; Johannessen, A.; Gulsvik, A.; Bakke, P.S.; Silverman, E.K.; DeMeo, D.L. Gender differences in COPD: Are women more susceptible to smoking effects than men? Thorax 2010, 65, 480–485. [CrossRef]

13. Bérubé, S.; Lemieux, J.; Moore, L.; Maunsell, E.; Brisson, J. Smoking at time of diagnosis and breast cancer-specific survival: New findings and systematic review with meta-analysis. Breast Cancer Res. 2014, 16, R42. [CrossRef] [PubMed]
14. Wu, A.H.; Gomez, S.L.; Vigen, C.; Kwan, M.L.; Keegan, T.H.; Lu, Y.; Shariff-Marco, S.; Monroe, K.R.; Kurian, A.W.; Cheng, I.; et al. The California Breast Cancer Survivorship Consortium (CBCSC): Prognostic factors associated with racial/ethnic differences in breast cancer survival. Cancer Causes Control. 2013, 24, 1821–1836. [CrossRef] [PubMed]

15. Braithwaite, D.; Izano, M.; Moore, D.H.; Kwan, M.L.; Tammemagi, M.C.; Hiatt, R.A.; Kerlikowske, K.; Kroenke, C.H.; Sweeney, C.; Habel, L.; et al. Smoking and survival after breast cancer diagnosis: A prospective observational study and systematic review. Breast Cancer Res. Treat. 2012, 136, 521–533. [CrossRef] [PubMed]

16. Nechuta, S.; Chen, W.Y.; Cai, H.; Poole, E.M.; Kwan, M.L.; Flatt, S.W.; Patterson, R.E.; Pierce, J.P.; Caan, B.J.; Ou Shu, X. A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. Int. J. Cancer 2016, 138, 2088–2097. [CrossRef] [PubMed]

17. Pierce, J.P.; Patterson, R.E.; Sengler, C.M.; Flatt, S.W.; Caan, B.J.; Natarajan, L.; Nechuta, S.J.; Poole, E.M.; Shu, X.O.; Chen, W.Y. Lifetime cigarette smoking and breast cancer prognosis in the After Breast Cancer Pooling Project. J. Natl. Cancer Inst. 2014, 106, djt359. [CrossRef] [PubMed]

18. Barnett, G.C.; Shah, M.; Redman, K.; Easton, D.F.; Ponder, B.A.; Pharoah, P.D. Risk factors for the incidence of breast cancer: Do they affect survival from the disease? J. Clin. Oncol. 2008, 26, 3310–3316. [CrossRef] [PubMed]

19. Sagiv, S.K.; Gaudet, M.M.; Eng, S.M.; Abrahamsson, P.E.; Shantakumar, S.; Teitelbaum, S.L.; Britton, J.A.; Bell, P.; Thomas, J.A.; Neugut, A.I.; et al. Active and passive cigarette smoke and breast cancer survival. Ann. Epidemiol. 2007, 17, 385–393. [CrossRef]

20. Murin, S.; Inciardi, J. Cigarette smoking and the risk of pulmonary metastasis from breast cancer. Chest 2001, 119, 1635–1640. [CrossRef]

21. Singh, S.; Pillai, S.; Chellappan, S. Nicotinic acetylcholine receptor signaling in tumor growth and metastasis. J. Oncol. 2011, 2011, 456743. [CrossRef] [PubMed]

22. Daniell, H.W.; Tam, E.; Filice, A. Larger axillary metastases in obese women and smokers with breast cancer—an influence by host factors on early tumor behavior. Breast Cancer Res. Treat. 1993, 25, 193–201. [CrossRef]

23. Duan, W.; Li, S.; Meng, X.; Sun, Y.; Jia, C. Smoking and survival of breast cancer patients: A meta-analysis of cohort studies. Breast Cancer Res. Treat. 2017, 33, 117–124. [CrossRef] [PubMed]

24. Hopenhayn, C.; Christian, W.J.; Christian, A.; Studts, J.; Mullet, T. Factors associated with smoking abstinence after diagnosis of early stage lung cancer. Lung Cancer 2019, 130, 55–61. [CrossRef] [PubMed]

25. Skeie, G.; Hjartåker, A.; Braaten, T.; Lund, E. Dietary change among breast and colorectal cancer survivors and cancer-free women in the Norwegian Women and Cancer cohort study. Cancer Causes Control. 2009, 20, 1955–1966. [CrossRef] [PubMed]

26. Hsieh, C.Y.; Su, C.C.; Shao, S.C.; Sung, S.F.; Lin, S.J.; Kao Yang, Y.H.; Lai, E.C. Taiwan’s National Health Insurance Research Database: Past and future. Clin. Epidemiol. 2019, 11, 349–358. [CrossRef] [PubMed]

27. Tsai, H.Y.; Chang, Y.L.; Chen, F.M. Effects of the COVID-19 pandemic on breast cancer screening in Taiwan. Breast 2020, 54, 52–55. [CrossRef] [PubMed]

28. Quan, H.; Sundararajan, V.; Halfon, P.; Fong, A.; Burnand, B.; Luthi, J.-C.; Saunders, L.D.; Beek, C.A.; Feasby, T.E.; Ghali, W.A. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med. Care 2005, 43, 1130–1139. [CrossRef] [PubMed]

29. Quan, H.; Li, B.; Couris, C.M.; Fushimi, K.; Graham, P.; Hider, P.; Januel, J.M.; Sundararajan, V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am. J. Epidemiol. 2011, 173, 676–682. [CrossRef]

30. Centers for Disease Control and Prevention; National Center for Chronic Disease Prevention and Health Promotion; Office on Smoking and Health. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General; Centers for Disease Control and Prevention (US): Atlanta, GA, USA, 2010.

31. Hecht, S.S. Tobacco smoke carcinogens and breast cancer. Environ. Mol. Mutagenesis 2002, 39, 119–126. [CrossRef]

32. Terry, P.D.; Rohan, T.E. Cigarette smoking and the risk of breast cancer in women: A review of the literature. Cancer Epidemiol. Biomark. Prev. 2005, 11, 953–971. [CrossRef] [PubMed]

33. Jones, M.E.; Schoemaker, M.J.; Wright, L.B.; Ashworth, A.; Swerdlow, A.J. Smoking and risk of breast cancer in the Generations Study cohort. Breast Cancer Res. 2017, 19, 18. [CrossRef] [PubMed]

34. Passarelli, M.N.; Newcomb, P.A.; Hampton, J.M.; Trentham-Dietz, A.; Titus, L.J.; Egan, K.M.; Baron, J.A.; Willett, W.C. Cigarette Smoking Before and After Breast Cancer Diagnosis: Mortality From Breast Cancer and Smoking-Related Diseases. J. Clin. Oncol. 2016, 34, 1315–1322. [CrossRef] [PubMed]

35. Kakugawa, Y.; Kawai, M.; Nishino, Y.; Fukamachi, K.; Ishida, T.; Ohuchi, N.; Minami, Y. Smoking and survival after breast cancer diagnosis in Japanese women: A prospective cohort study. Cancer Sci. 2015, 106, 1066–1074. [CrossRef] [PubMed]

36. Jizzini, M.; Raghavendra, A.S.; Ibrahim, N.K.; Kypriotakis, G.; Cinciripini, P.M.; Seoudy, K.; Karam-Hage, M.A. The impact of smoking cessation on breast cancer patients’ survival. J. Clin. Oncol. 2019, 37, 1542. [CrossRef]

37. Hellmann, S.S.; Thysken, L.C.; Tostrup, J.S.; Grønbaek, M. Modifiable risk factors and survival in women diagnosed with primary breast cancer: Results from a prospective cohort study. Eur. J. Cancer Prev. 2010, 19, 366–373. [CrossRef] [PubMed]

38. Izano, M.; Satariano, W.A.; Hiatt, R.A.; Braithwaite, D. Smoking and mortality after breast cancer diagnosis: The health and functioning in women study. Cancer Med. 2015, 4, 315–324. [CrossRef] [PubMed]

39. Ministry of Health and Welfare. 2020 Taiwan Health and Welfare Report; Ministry of Health and Welfare: Taipei, Taiwan, 2020.

40. Jassem, J. Tobacco smoking after diagnosis of cancer: Clinical aspects. Transl. Lung Cancer Res. 2019, 8, s50–s58. [CrossRef]
41. Peppone, L.J.; Mustian, K.M.; Morrow, G.R.; Dozier, A.M.; Ossip, D.J.; Janelins, M.C.; Sprod, L.K.; McIntosh, S. The effect of cigarette smoking on cancer treatment-related side effects. *Oncologist* 2011, 16, 1784–1792. [CrossRef]

42. Kaufman, E.L.; Jacobson, J.S.; Hershman, D.L.; Desai, M.; Neugut, A.I. Effect of breast cancer radiotherapy and cigarette smoking on risk of second primary lung cancer. *J. Clin. Oncol.* 2008, 26, 392–398. [PubMed] [CrossRef]

43. Wong, G.; Lam, E.; Karam, I.; Yee, C.; Drost, L.; Tam, S.; Lam, H.; McCarvell, A.; McKenzie, E.; Chow, E. The impact of smoking on adjuvant breast cancer radiation treatment: A systematic review. *Cancer Treat Res. Commun.* 2020, 24, 100185. [CrossRef]

44. Zhang, J.; Kamdar, O.; Le, W.; Rosen, G.D.; Upadhyay, D. Nicotine induces resistance to chemotherapy by modulating mitochondrial signaling in lung cancer. *Am. J. Respir. Cell Mol. Biol.* 2009, 40, 135–146. [CrossRef] [PubMed]

45. O’Malley, M.; King, A.N.; Conte, M.; Ellingrod, V.L.; Ramnath, N. Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. *J. Thorac. Oncol.* 2014, 9, 917–926. [CrossRef]

46. Goodwin, S.J.; McCarthy, C.M.; Pusic, A.L.; Buu, D.; Howard, M.; Disa, J.J.; Cordeiro, P.G.; Mehrara, B.J. Complications in smokers after postmastectomy tissue expander/implant breast reconstruction. *Ann. Plast. Surg.* 2005, 55, 16–19, discussion 19–20. [PubMed] [CrossRef]

47. Padubidri, A.N.; Yetman, R.; Browne, E.; Lucas, A.; Papay, F.; Larive, B.; Zins, J. Complications of postmastectomy breast reconstructions in smokers, ex-smokers, and nonsmokers. *Plast. Reconstr. Surg.* 2001, 107, 342–349. [PubMed] [CrossRef]

48. Boone, S.D.; Baumgartner, K.B.; Baumgartner, R.N.; Connor, A.E.; John, E.M.; Giuliano, A.R.; Hines, L.M.; Rai, S.N.; Riley, E.C.; Pinkston, C.M.; et al. Active and passive cigarette smoking and mortality among Hispanic and non-Hispanic white women diagnosed with invasive breast cancer. *Ann. Epidemiol.* 2015, 25, 824–831. [PubMed] [CrossRef]

49. Key, T.J.; Allen, N.E.; Spencer, E.A.; Travis, R.C. Nutrition and breast cancer. *Breast* 2003, 12, 412–416. [CrossRef]

50. Brand, J.S.; Chan, M.F.; Dowsett, M.; Folkard, E.; Wareham, N.J.; Luben, R.N.; van der Schouw, Y.T.; Khaw, K.T. Cigarette smoking and endogenous sex hormones in postmenopausal women. *J. Clin. Endocrinol. Metab.* 2011, 96, 3184–3192. [CrossRef]

51. Wartenberg, D.; Calle, E.E.; Thun, M.J.; Heath, C.W., Jr.; Lally, C.; Woodruff, T. Passive smoking exposure and female breast cancer mortality. *J. Natl. Cancer Inst.* 2000, 92, 1666–1673. [CrossRef]

52. Parada, H., Jr.; Bradshaw, P.T.; Engel, L.S.; Conway, K.; Steck, S.E.; Teitelbaum, S.L.; Neugut, A.I.; Santella, R.M.; Gammon, M.D. Environmental Tobacco Smoke Exposure and Survival Following Breast Cancer. *Cancer Epidemiol. Biomark. Prev.* 2017, 26, 270–280. [PubMed] [CrossRef]

53. Chiang, C.Y.; Chang, H.Y. A population study on the time trend of cigarette smoking, cessation, and exposure to secondhand smoking from 2001 to 2013 in Taiwan. *Popul. Health Metr.* 2016, 14, 38. [CrossRef]