Time-dependent risks of cancer clustering among couples: a nationwide population-based cohort study in Taiwan

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ABSTRACT

Objectives Spousal clustering of cancer warrants attention. Whether the common environment or high-age vulnerability determines cancer clustering is unclear. The risk of clustering in couples versus non-couples is undetermined. The time to cancer clustering after the first cancer diagnosis is yet to be reported. This study investigated cancer clustering over time among couples by using nationwide data.

Methods A cohort of 5643 married couples in the 2002–2013 Taiwan National Health Insurance Research Database was identified and randomly matched with 5643 non-couple pairs through dual propensity score matching. Factors associated with clustering (both spouses with tumours) were analysed by using the Cox proportional hazard model.

Results Propensity-matched analysis revealed that the risk of clustering of all tumours among couples (13.70%) was significantly higher than that among non-couples (11.84%) (OR=1.182, 95% CI 1.058 to 1.321, P=0.0031). The median time to clustering of all tumours and of malignant tumours was 2.92 and 2.32 years, respectively. Risk characteristics associated with clustering included high age and comorbidity.

Conclusions Shared environmental factors among spouses might be linked to a high incidence of cancer clustering. Cancer incidence in one spouse may signal cancer vulnerability in the other spouse. Promoting family-oriented cancer care in vulnerable families and preventing shared lifestyle risk factors for cancer are suggested.

INTRODUCTION

Genetic susceptibilities have been considered risk factors of cancer among family members.1 However, previous studies have reported the clustering of cancer among married couples who did not share genetic relatedness. Family clustering of cancer develops when the occurrence of cancer within a family exceeds the expected occurrence in the population.1 Prior related research has indicated that several types of cancer, including lung, stomach, skin and upper aerodigestive tract cancer, could aggregate within couples because of shared exposure such as smoking and ultraviolet radiation.2 3 Moreover, high age was closely related to high odds of cancer among long-standing spouses.4 This association was explained by the presence of chronic conditions including obesity and diabetes after midlife.5 Whether the shared exposure or high-age vulnerability determines cancer clustering is uncertain. Hence, the risk comparison of cancer clustering between couples and non-couples is highly demanded. Most clustering studies have reported univariate statistics of ratios or have examined a relatively small number of associated factors of cancer. Cancer clustering studies are especially lacking in Asian countries, where environmental exposures are presumably different from those in Western countries.6 Frequently diagnosed cancers in highly industrialised Taiwan include lung, liver, colorectal, breast and oral cancers,7 which can be related to infectious agents. Overall, lung cancer rates in Asia exceed the rates in the USA and European countries.8 Moreover, physical inactivity and diet continue...
to affect Taiwan as they do in North America and Europe.\textsuperscript{8,9} To improve the understanding of cancer clustering in couples, investigating the factors associated with the risk of cancer for each individual spouse is imperative. Previous studies have indicated sex differences in cancer; men were associated with a higher risk of oral cancer than women,\textsuperscript{10} whereas women might be more vulnerable to lung cancer development than men.\textsuperscript{11} Different occupations have been associated with different types and risks of cancer\textsuperscript{12,13} because exposure to various hazards such as pesticides and wood dusts may vary by occupation.\textsuperscript{14} Moreover, specific medical conditions led to the subsequent occurrence of cancer; for example, type 2 diabetes was associated with lung cancer, and obesity was associated with nervous system cancer.\textsuperscript{15,16} Income, urbanisation and the use of carcinogenic medication have been discussed in prior research.\textsuperscript{17–19} However, the findings regarding the effects on cancer remain inconclusive. The effects of cancer risk factors on cancer clustering require investigation.

Cancer incidence in one spouse may signal cancer in the other spouse because of their common environment through which certain malignancies, including liver cancers and nasopharyngeal carcinoma, can be virally transmitted.\textsuperscript{20,21} However, a knowledge gap exists regarding the time interval between the diagnosis of cancer in one spouse and the subsequent onset of cancer in the other spouse. Furthermore, all previous clustering studies have used observational cohort data which lack a control group and thus do not increase the strength of inferential evidence. Therefore, this study investigated risk factors of cancer clustering and analysed the time to clustering in married couples by using nationally representative data. In addition, the odds of cancer clustering in couples versus non-couples were compared.

METHODS

Hypothesis and research design

This study hypothesised that the time-dependent risk of cancer clustering among couples is associated with both individual and shared characteristics of spouses. In addition, the central hypothesis is that a common family environment leads to greater odds of cancer among couples than among otherwise similar non-couple pairs. A longitudinal population-based design was used to test both hypotheses by analysing nationwide data of couples versus matched pairs of individuals in Taiwan. The study was approved by the Research Ethics Committee at China Medical University and Hospital, Taiwan, under no. CMUH103-REC3-095.

Data source and study sample

This was a retrospective study analysing data extracted from the 2002–2013 National Health Insurance (NHI) Research Database (NHIRD), which comprises data for 1 million randomly sampled beneficiaries and thus fully represents enrollees in Taiwan (n=23.50 million). The NHIRD is maintained by the National Health Research Institutes of Taiwan and contains all the original medical claims under the universal NHI programme.

Married couples were identified from the NHI registry. Only when two individuals registered their marriage and possessed a relationship of an insured and dependent spouse (a spouse who depends on the health insurance of the other spouse) were they regarded as a couple. To ascertain an initial diagnosis of a tumour throughout the longitudinal period, patients diagnosed with a tumour (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 140.x–239.x) in 2002 were excluded from the study. The ICD-9-CM codes of malignant tumours range from 140 to 208. Overall, 2003–2013 was the follow-up period. Because of missing data, 43 patients were excluded. Consequently, a cohort of 5643 married couples, comprising 11286 individuals (5643 insured spouses and 5643 dependent spouses) was identified for the analysis. Five thousand six hundred and forty-three were all the couples identifiable in the NHIRD.

To ensure comparability of couples (cases) and non-couples (controls), non-coupled individuals were randomly selected to constitute the control group, which was matched by the identical single value of sex, age and comorbidity with the case group. The 1:1 propensity score matching (PSM) method, a popular approach to reduce selection bias in clinical studies, was used to alleviate baseline differences between couples and non-couples in covariate values.\textsuperscript{22,23} The same procedure was performed twice for each of the two spouses to obtain two non-couple counterparts (four total individuals in the matching). This novel implementation was named dual PSM. In dual PSM, three matched variables are subsequently tested twice. The couples and the propensity score-matched non-couples were not significantly different in sex, age and comorbidity (all P>1), indicating an effective matching of the case and control groups. Propensity score analysis provides an alternative to multivariate analyses through adjustment for possible confounders.\textsuperscript{24} Finally, 5643 couples and 5643 non-couples were eligible for subsequent analysis.

Variables

The units of analysis in this study were the individual and the pair. The clustering of cancer served as a dichotomous outcome variable, with the dates of cancer diagnosis analysed for both spouses. The duration until the clustering of cancer within a couple after a certain cancer diagnosis in the first spouse was defined on a continuous scale with days as the smallest unit. Clustering in this study refers only to a clinical state in which both the insured and dependent spouses were diagnosed with any of the ICD-9-CM tumour codes 140.x through 239.x, including concordant and discordant cancer types.

On the basis of the aforementioned studies, the present research grouped the following independent variables possibly associated with cancer occurrence into two categories: (1) insured spouse characteristics: sex, age,
occupation, premium-based monthly salary, comorbidity, catastrophic illness and injury, use of carcinogenic medication, region and urbanisation level; (2) dependent spouse characteristics: age, comorbidity, catastrophic illness and injury and use of carcinogenic medication. Because spouses lived as a couple, region and urbanisation level were regarded as shared environment characteristics of the couples. The remaining variables were the characteristics of the individual spouses. Because the Taiwan government solely allows opposite-sex marriage, only the sex of the insured spouse was adopted to eliminate predictable collinearity. Age did not pass the normality test and thus was classified into five ordinal levels, according to the frequency distribution. Occupation, premium-based monthly salary, catastrophic illness and injury and region were defined according to the official classifications of the NHI programme. The Bureau of National Health Insurance issues the Catastrophic Illness and Injury card to patients with severe illness or injury (such as end-stage kidney disease or permanent disability) after the diagnosis is verified and signed by a board-certified physician. Comorbidity was calculated using the Charlson Comorbidity Index (CCI), a frequently used instrument in clinical research. Following an original scoring from 0 to 6 by weighting ICD-9-CM codes for each spouse, this study classified comorbidity into categories of 0 (without comorbidity), 1, 2 and 3 (with high comorbidity) because of the low frequency distribution of CCI scores higher than 3. Urbanisation level was assessed using a five-level scale, with levels 1 and 5 indicating the highest and lowest urbanisation levels, respectively. Receipt of any of the following medicines was considered the use of carcinogenic medication: troglitazone, rosiglitazone, pioglitazone and zolpidem. The 13 independent variables were measured on either an ordinal or a categorical level.

The variables in the case–control comparison were all in the pair level (couples vs non-couple pairs). As mentioned, individual members of each couple were matched to non-couples on the basis of their characteristics through dual PSM; thus, no variables besides couple status were used to examine the clustering.

**Data analysis**

The statistical methods employed were the χ² test, time-to-event analysis and logistic regression. The χ² test was used to examine the observed values of prevalence for bivariate associations. Time-to-event analysis was used to predict the time-dependent risk of cancer clustering. Therefore, the time to clustering of cancer (TCC) was calculated and incorporated into the time-to-event analysis. The Cox proportional hazard model, the most common time-to-event method, was mainly employed for multivariate analysis, with the adjusted HR being reported. The case-control matched analysis was performed using logistic regression, with the OR being reported. Moreover, collinearity diagnostics was conducted using indices including variance inflation and tolerance to detect any significantly high interrelation of characteristics between the two spouses. All tests were two sided and were conducted using an alpha value of 0.05. Data were analysed using SAS V.9.4 (SAS Institute).

**RESULTS**

Table 1 illustrates that the majority of the couples were aged 45–54 years (26.56%); however, elderly people accounted for nearly one-fifth of all the couples (19.39%). Most couples had no comorbidities (85.60%); and slightly more than one-tenth scored 1 for the CCI (12.79%). Most of the couples were not issued the catastrophic illness and injury card (91.29%) by the health authorities. Slightly more than 2% of the couples used carcinogenic medication (2.17%). Detailed characteristics of the insured spouses and dependent spouses are reported in table 2. The majority of insured spouses were private employees and government employees (51.11%), with a premium-based monthly salary ≤US$760 (64.31%), residing in the Taipei region (35.17%) and in areas graded the highest level of urbanisation (31.04%). Moreover, the prevalence rate of cancer clustering among the studied couples was 13.70% (table 2).

The χ² test indicated that age, monthly income, comorbidity and catastrophic illness and injury were significantly associated with cancer clustering among the couples (table 2, all P<0.01). Specifically, high age (≥65 years), high comorbidity (CCI≥3) and the presence of a catastrophic illness or injury were significantly associated with a high prevalence of cancer clustering for both insured spouses and dependent spouses.

| Table 1 Characteristics of couples (n=5643 couples) |
|-----------------|-----------------|-----------------|
| **Variables**   | **Frequency**   | **%**           |
| **Age**         |                 |                 |
| 16–34 years     | 1033            | 9.15            |
| 35–44 years     | 2730            | 24.19           |
| 45–54 years     | 2998            | 26.56           |
| 55–64 years     | 2337            | 20.71           |
| ≥65 years       | 2188            | 19.39           |
| **Comorbidity (CCI)** |          |                 |
| 0               | 9961            | 85.60           |
| 1               | 1443            | 12.79           |
| ≥2              | 96              | 0.85            |
| ≥3              | 86              | 0.76            |
| **Catastrophic illness and injury** |          |                 |
| Absent          | 10303           | 91.29           |
| Present         | 983             | 8.71            |
| **Use of carcinogenic medication** |          |                 |
| No              | 11041           | 97.83           |
| Yes             | 245             | 2.17            |

CCI, Charlson Comorbidity Index.
Table 2  Cancer clustering among couples, by characteristics of insured spouses and dependent spouses (χ² test, n=5643 couples)

| Variables | Frequency | % | No clustering of cancer | Clustering of cancer | χ² | P value |
|-----------|-----------|---|-------------------------|----------------------|-----|---------|
|           | n₁       | n₂ |                         |                      |     |         |
| Total     | 4870     | 773 | 86.30                   | 13.70                |     |         |
| Insured spouse characteristics | | | | | | |
| Sex       |          |    |                         |                      |     |         |
| Female    | 1460     | 1271 | 25.87                   | 87.05                | 0.3310 | 12.95   |
| Male      | 4183     | 3599 | 74.13                   | 86.04                | 584  | 13.96   |
| Age       |          |    |                         |                      |     |         |
| 16–34 years | 379     | 345 | 6.72                    | 91.03                | 0.3310 | 8.97    |
| 35–44 years | 1295  | 1141 | 22.95                   | 88.11                | 154  | 11.89   |
| 45–54 years | 1607  | 1407 | 28.48                   | 87.55                | 200  | 12.45   |
| 55–64 years | 1185  | 1013 | 21.00                   | 85.49                | 172  | 14.51   |
| ≥65 years | 1177     | 964 | 20.86                   | 81.90                | 213  | 18.10   |
| Occupation |          |    |                         |                      |     |         |
| First category (private employee and government employee) | 2884 | 2498 | 51.11                   | 86.62                | 386  | 13.38   |
| Second category (labour union member) | 785 | 687 | 13.91                   | 87.52                | 98   | 12.48   |
| Third category (farmer and fisherman) | 695 | 596 | 12.32                   | 85.76                | 99   | 14.24   |
| Fourth, fifth and sixth categories (soldier, social security insured and veteran and religious group member) | 1279 | 1089 | 22.67                   | 85.14                | 190  | 14.86   |
| Premium-based monthly salary (US$) |          |    |                         |                      |     |         |
| ≤760      | 3629     | 3157 | 64.31                   | 86.99                | 472  | 13.01   |
| 760–960   | 413      | 365 | 7.32                    | 88.98                | 48   | 11.62   |
| 960–1210  | 481      | 414 | 8.52                    | 86.07                | 67   | 13.93   |
| 1210–1526 | 473      | 414 | 8.30                    | 86.07                | 67   | 13.93   |
| >1526     | 647      | 527 | 11.47                   | 81.45                | 120  | 18.55   |
| Comorbidity (CCI) |          |    |                         |                      |     |         |
| 0         | 4831     | 4219 | 85.61                   | 87.33                | 612  | 12.67   |
| 1         | 731      | 589 | 12.95                   | 80.57                | 142  | 19.43   |
| 2         | 42       | 35  | 0.74                    | 83.33                | 7    | 16.67   |
| ≥3        | 39       | 27  | 0.69                    | 69.23                | 12   | 30.77   |
| Catastrophic illness and injury |          |    |                         |                      |     |         |
| Absent    | 5106     | 4463 | 90.48                   | 87.41                | 643  | 12.59   |
| Present   | 537      | 407 | 9.52                    | 75.79                | 130  | 24.21   |
| Use of carcinogenic medication |          |    |                         |                      |     |         |
| No        | 5537     | 4783 | 98.12                   | 86.38                | 754  | 13.62   |
| Yes       | 106      | 87  | 1.88                    | 82.08                | 19   | 17.92   |
| Region    |          |    |                         |                      |     |         |
| Taipei    | 1980     | 1699 | 35.17                   | 85.81                | 281  | 14.19   |
| Northern  | 869      | 760 | 15.44                   | 87.46                | 109  | 12.54   |
| Central   | 1076     | 933 | 19.12                   | 86.71                | 143  | 13.29   |
| Southern  | 752      | 637 | 13.36                   | 84.71                | 115  | 15.29   |
| Southeast | 847      | 741 | 15.05                   | 87.49                | 106  | 12.51   |
| Eastern   | 105      | 89  | 1.87                    | 84.76                | 16   | 15.24   |

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spouses. Furthermore, insured spouses of the highest
monthly income bracket (>US$1526) were more likely
to develop cancer clustering. No significant collinearity
was detected.

The Cox proportional hazard model used no clus-
tering of cancer as a referent of the outcome variable
for all levels of analysis. The unadjusted analysis indi-
cated that five variables were significantly associated with
cancer clustering among the couples (table 3, all P < 0.05).
However, after holding all other covariates constant, six
variables were found to be significant factors of cancer
clustering (all P < 0.05). Compared with the lowest income
group (<US$760), insured spouses of the highest monthly
income level (>US$1526) were significantly more likely
to experience cancer clustering (HR=1.484, 95% CI 1.133
to 1.944). Compared with insured spouses with no
comorbidities (CCI=0), insured spouses with CCI=1 were
significantly more likely to be involved in cancer clustering
(HR=1.293, 95% CI 1.065 to 1.571). The risk of cancer
clustering was significantly higher in insured spouses with
catastrophic illness and injury than in insured spouses
without them (HR=1.471, 95% CI 1.192 to 1.815). Compared
with insured spouses residing in Taipei, those residing in the southern region had a significantly higher risk of cancer clustering (HR=1.393, 95% CI 1.071 to 1.811). Dependent spouses aged 35–44
years were significantly more likely to experience cancer clustering (HR=1.440, 95% CI 1.010 to 2.053) than those in the
youngest age group (16–34 years). The risk of cancer clus-
tering was significantly higher in dependent spouses with
catastrophic illness and injury than in dependent spouses
without them (HR=1.374, 95% CI 1.096 to 1.722). In this
study, the proportionality assumption of the Cox model
was satisfied.

In addition to the factors associated with cancer
clustering, the Cox analysis revealed that the median
TCC was 2.92 years (SD=2.55, range=0–10.85) among
spouses with all types of tumours, whereas the TCC was
2.32 years (SD=2.25, range=0–8.04) for all malignant
tumours.

Table 2

| Variables                        | Frequency | %    | No clustering of cancer | χ² | Clustering of cancer | P value |
|----------------------------------|-----------|------|-------------------------|----|----------------------|---------|
|                                  |           |      | n₁ | %  | n₂ | %  |                |        |
| Urbanisation level               |           |      |    |    |    |    |                |        |
| Level 1 (highest)                | 1745      | 31.04| 1491 | 85.44| 254 | 14.56| 0.1874        |        |
| Level 2                          | 1665      | 29.62| 1426 | 85.65| 239 | 14.35|            |        |
| Level 3                          | 954       | 16.97| 841  | 88.16| 113 | 11.84|            |        |
| Level 4                          | 739       | 13.14| 636  | 86.06| 103 | 13.94|            |        |
| Level 5 (lowest)                 | 519       | 9.23 | 458  | 88.25| 61  | 11.75|            |        |
| Dependent spouse characteristics |           |      |    |    |    |    |                |        |
| Age                              |           |      |    |    |    |    |                |        |
| 16–34 years                      | 654       | 11.59| 600  | 91.74| 54  | 8.26 | <0.0001       |        |
| 35–44 years                      | 1435      | 25.43| 1266 | 88.22| 169 | 11.78|            |        |
| 45–54 years                      | 1391      | 24.65| 1196 | 85.98| 195 | 14.02|            |        |
| 55–64 years                      | 1152      | 20.41| 972  | 84.38| 180 | 15.63|            |        |
| ≥65 years                        | 1011      | 17.92| 836  | 82.69| 175 | 17.31|            |        |
| Comorbidity (CCI)                |           |      |    |    |    |    |                |        |
| 0                                | 4830      | 85.59| 4194 | 86.83| 636 | 13.17| 0.0048*       |        |
| 1                                | 712       | 12.62| 597  | 83.85| 115 | 16.15|            |        |
| 2                                | 54        | 0.96 | 45   | 83.33| 9   | 16.67|            |        |
| ≥3                               | 47        | 0.83 | 34   | 72.34| 13  | 27.66|            |        |
| Catastrophic illness and injury  |           |      |    |    |    |    |                |        |
| Absent                           | 5197      | 92.10| 4531 | 87.18| 666 | 12.82| <0.0001       |        |
| Present                          | 446       | 7.90 | 339  | 76.01| 107 | 23.99|            |        |
| Use of carcinogenic medication   |           |      |    |    |    |    |                |        |
| No                               | 5504      | 97.54| 4757 | 86.43| 747 | 13.57| 0.0822        |        |
| Yes                              | 139       | 2.46 | 113  | 81.29| 26  | 18.71|            |        |

*p < 0.05.
CCI, Charlson Comorbidity Index.
Table 3  Association between spousal characteristics and cancer clustering among couples, with adjustment for all other characteristics (Cox proportional hazard model, n=5643 couples)

| Variables                                         | Unadjusted model |                                            | Adjusted model |                                            |
|---------------------------------------------------|------------------|---------------------------------------------|----------------|---------------------------------------------|
|                                                   | Crude HR         | 95% CI | P value | Adjusted HR | 95% CI | P value |
| Insured spouse characteristics                    |                  |        |         |             |        |         |
| Sex                                               |                  |        |         |             |        |         |
| Female (referent)                                 | –                | –      | –       | –           | –      | –       |
| Male                                              | 1.120            | 0.950 to 1.321 | 0.1770 | 1.062       | 0.883 to 1.276 | 0.5222 |
| Age                                               |                  |        |         |             |        |         |
| 16–34 years (referent)                            | –                | –      | –       | –           | –      | –       |
| 35–44 years                                      | 1.159            | 0.799 to 1.682 | 0.4356 | 0.849       | 0.553 to 1.305 | 0.4556 |
| 45–54 years                                      | 1.110            | 0.771 to 1.597 | 0.5752 | 0.730       | 0.457 to 1.166 | 0.1882 |
| 55–64 years                                      | 1.366            | 0.945 to 1.974 | 0.0969 | 0.847       | 0.498 to 1.439 | 0.5394 |
| ≥65 years                                         | 1.578            | 1.099 to 2.267 | 0.0135*| 0.972       | 0.537 to 1.759 | 0.9245 |
| Occupation                                        |                  |        |         |             |        |         |
| First category (private employee and government employee) (referent) | – | – | – | – | – | – |
| Second category (labour union member)             | 0.969            | 0.776 to 1.210 | 0.7807 | 1.101       | 0.842 to 1.439 | 0.4823 |
| Third category (farmer and fisherman)             | 1.193            | 0.956 to 1.488 | 0.1188 | 1.357       | 0.995 to 1.851 | 0.0538 |
| Fourth, fifth and sixth categories (soldier, social security insured and veteran and religious group member) | 1.169 | 0.982 to 1.392 | 0.0783 | 1.235       | 0.959 to 1.591 | 0.1017 |
| Premium-based monthly salary (US$)                |                  |        |         |             |        |         |
| ≤760 (referent)                                   | –                | –      | –       | –           | –      | –       |
| 760–960                                           | 0.895            | 0.665 to 1.205 | 0.4653 | 1.085       | 0.779 to 1.511 | 0.6300 |
| 960–1210                                          | 0.905            | 0.700 to 1.170 | 0.4463 | 1.090       | 0.804 to 1.477 | 0.5782 |
| 1210–1526                                         | 0.963            | 0.742 to 1.251 | 0.7803 | 1.211       | 0.884 to 1.658 | 0.2332 |
| >1526                                             | 1.218            | 0.997 to 1.489 | 0.0536 | 1.484       | 1.133 to 1.944 | 0.0042*|
| Comorbidity (CCI)                                 |                  |        |         |             |        |         |
| 0 (referent)                                      | –                | –      | –       | –           | –      | –       |
| 1                                                 | 1.373            | 1.534 to 1.648 | 0.0007*| 1.293       | 1.065 to 1.571 | 0.0094*|
| 2                                                 | 1.097            | 0.521 to 2.312 | 0.8074 | 0.930       | 0.437 to 1.978 | 0.8504 |
| ≥3                                                | 1.534            | 0.866 to 2.717 | 0.1424 | 1.123       | 0.620 to 2.035 | 0.7026 |
| Catastrophic illness and injury                   |                  |        |         |             |        |         |
| Absent (referent)                                 | –                | –      | –       | –           | –      | –       |
| Present                                           | 1.513            | 1.251 to 1.829 | <0.0001*| 1.471       | 1.192 to 1.815 | 0.0003*|
| Use of carcinogenic medication                    |                  |        |         |             |        |         |
| No (referent)                                     | –                | –      | –       | –           | –      | –       |
| Yes                                               | 1.257            | 0.797 to 1.984 | 0.3251 | 1.022       | 0.638 to 1.636 | 0.9294 |
| Region                                            |                  |        |         |             |        |         |
| Taipei (referent)                                 | –                | –      | –       | –           | –      | –       |
| Northern                                          | 1.005            | 0.806 to 1.254 | 0.9630 | 1.084       | 0.843 to 1.393 | 0.5304 |
| Central                                           | 1.027            | 0.840 to 1.256 | 0.7963 | 1.143       | 0.909 to 1.438 | 0.2536 |
| Southern                                          | 1.218            | 0.979 to 1.514 | 0.0764 | 1.393       | 1.071 to 1.811 | 0.0133*|
| Southeast                                         | 0.979            | 0.783 to 1.225 | 0.8529 | 1.053       | 0.828 to 1.338 | 0.6742 |
| Eastern                                           | 1.393            | 0.841 to 2.306 | 0.1976 | 1.446       | 0.853 to 2.450 | 0.1710 |

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Table 4 presents the results of the $\chi^2$ test and logistic regression, both in couple-level analysis through dual PSM. The $\chi^2$ test results indicated that coupled relation was significantly associated with cancer clustering ($P=0.0031$). The percentage of clustering among the couples was significantly higher than that among the non-couples (13.70% vs 11.84%). The results of the logistic regression revealed that, after 1:1 dual PSM for sex, age and CCI, coupled relation was significantly associated with cancer clustering (OR=1.182, 95% CI 1.058 to 1.321, $P=0.0031$). The odds of cancer clustering among couples were significantly higher than those among non-couple matched pairs. Because the couples and non-couple pairs had been matched, no additional analyses were performed.
DISCUSSION

High spousal proportion of cancer

Familial proportion, the percentage of familial cancers calculated according to the family population, was proposed by Hemminki et al. Derived from this concept, spousal proportion was adopted by this study to represent the prevalence rate of the clustering of tumours among all married couples. The determined spousal proportion was 13.70% (773/5,643), a prevalence rate markedly higher than that of non-couple pairs (11.84%). Only 7.63% of the clustering (59/773) were concordant types; the finding that most of the tumours in couples were discordant types (92.37%) is similar to that of previous studies. Ranked by spousal proportion, the top-two concordant types were skin and oral tumours (0.74% and 0.41%), ICD-9-CM 170–175 and 140–149, respectively. Notably, betel nut chewing has been identified as a risk factor of oral cancer in Taiwan. The spousal proportion of malignant tumours was 1.01% (57/5,643), also higher than the corresponding 0.82% of the control group. A previously recorded nationwide prevalence rate of cancer clustering that could be compared with the current findings is lacking. However, prior research has reported that colorectal cancers accounted for the highest proportion of site-specific familial cancers at 12.80%. Further, previous studies have reported increased risks of concordant cancers among spouses by using standardised incidence ratios (SIRs). For example, SIRs ranged from 1.24 to 1.97 for lung, upper aerodigestive tract and skin cancers and from 1.19 to 1.38 for stomach, lung and bladder cancers.

Previous studies have considered the clustering phenomenon of diseases to be the result of ‘assortative mating’ and ‘cohabitation effects’. Through reciprocal marital relationships, the initial similarity between spouses can further expand to the gradual concordance of health behaviours and lifestyle in a common family environment. This tendency towards concordant behaviours is evident in Asian collectivism-prone cultures. Similarity in lifestyle explains the clustering of cancer. Furthermore, studies indicated that certain incidences of malignancies were engendered by viral infections transmitted through close contact. By contrast, non-couples, who did not share the aforementioned familial factors, exhibited a considerably low prevalence rate of cancer clustering. Hence, identifying the risk factors attributable to cancer development from a common environment and emphasising avoidable exposures and modifiable risk behaviours are the health policy priority.

Personal characteristics predicting risk of clustering among couples

Six individual characteristics were identified as predictors of cancer clustering among couples: income, comorbidity, catastrophic illness and injury and region of the insured spouse and age and catastrophic illness and injury of the dependent spouse. These findings demonstrate that individual characteristics explain the development of cancer clustering among couples. Although the category of occupation was not deemed a factor of cancer clustering in this study, region was, indicating a geographical health disparity in cancer. This geographical disparity, engendered partially by variation in exposure to environmental carcinogens, warrants attention from health policy-makers, especially for the manufacturing plants concentrated in the southern region. Insured spouses in the highest income level were associated with a higher risk of the clustering of all tumours. After conducting additional analysis, however, this study revealed that low income was associated with a high prevalence of clustering of malignant tumours (the lowest income group accounted for 70.18% of all malignant tumours), which is consistent with relevant literature. The effects of socioeconomic status on cancer substantiate the need for future research. In unadjusted analysis, insured spouses aged ≥65 years and dependent spouses aged 35–44, 55–64 and ≥65 years had high risks of experiencing cancer clustering. However, dependent spouses aged 35–44 years were the high-risk group by age after adjustment for all other factors. Most of the dependent spouses in this study were female (74.13%). Previous studies have reported that the onset of breast cancer occurred mainly at a young age (≤45 years) among those with a familial risk of breast cancer; the peak onset age of breast and ovarian cancers was between 35 and 50 years among female mutation carriers in Asia. Overall, the finding that the risk of cancer was higher at higher ages echoes previous studies and can be explained by likely chronic conditions. However, the onset age of certain cancers has decreased according to extant literature and thus warrants attention.

The effect of common environments and personal characteristics on the development of cancer clustering substantially parallels ecological system theory. The microsystem (individual) and mesosystem (family and neighbourhood), as the two cores of the ecological system, both contribute to the formation of cancer clusters among couples and require comprehensive assessment for cancer epidemiology. The study findings warrant the prevention of shared lifestyle risk factors for cancer among couples. Future research should concentrate on investigating the spousal proportion of a specific cancer by using the identified risk factors.

Time-dependent clustering of cancer

To our knowledge, this is the first study that investigated clustering of cancer in a case–control comparison and measured the duration until the occurrence of cancer in both spouses after the first diagnosis of cancer in one spouse. The median TCC was 2.32 years for the clustering of all malignant tumours, which was shorter than the TCC of all tumours. The 2.32-year TCC may indicate the progressive nature of malignant tumours or the high awareness of symptoms among spouses in shared environments, who seek medical care earlier; thus, it provides useful implications for cancer care.
Limitations of this study stem from the administrative database used. First, the NHIRD does not include information on family history of cancer, health behavior and lifestyle and carcinogetic products; the absence of such information might attenuate the statistical testing power. Nevertheless, this study exploited all obtainable data for analysis. Second, previous marriage (widowed or divorced), cohabitation, the duration of cohabitation and the timing of the cancer diagnosis relative to marriage could not be ascertained from the secondary data, thus limiting further analysis in this study. Third, the time period of follow-up was not lifetime; the average age of the study cohort might not yet reach the peak age of cancer incidence (approximately 70 years of age). The generalisability of the findings is therefore more applicable to spouses of younger age. Finally, spouses identified from the database were limited to the insured-dependent relationship. Extrapolation of the study findings to all other circumstances requires caution.

CONCLUSIONS
Considering the cohort, case–control approach and the individual and couple analyses, this population-based study substantively contributes to the knowledge base by reporting the pivotal role of common family environments in the high clustering of cancers, demonstrating that individual spousal characteristics predict clustering and determining the TCC among couples. A cancer diagnosis in one spouse may imply vulnerability in both spouses and warrants timely intervention after the first diagnosis. The findings justify the necessity of promoting family-based cancer care.

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Contributors J-YW proposed the study idea, designed the study, interpreted the analysis and wrote the first draft of the manuscript. Y-WL contributed in critical discussion and edited the manuscript. C-SL reviewed and performed the statistical analyses. C-CY reviewed and revised the manuscript. C-YW participated in critical discussion and edited the manuscript. C-YW contributed to the study design and revised the manuscript. C-CY contributed to the literature review and wrote the first draft of the manuscript. Y-WL contributed to the literature review and determined the TCC among couples. A cancer diagnosis in one spouse may imply vulnerability in both spouses and warrants timely intervention after the first diagnosis. The findings justify the necessity of promoting family-based cancer care.

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