Title: Second primary cancers following cancer among adolescents and young adults in Queensland, Australia, 1982-2013.

Short title: Second primary cancer in AYA cancer survivors

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Abstract

Purpose: Increased risk of second primary cancers is an unwanted consequence of cancer survivorship. While the epidemiology of second cancers is well-documented for children and older people, less is known about the full range of second cancers following cancer among adolescents and young adults (AYAs).

Methods: Unit record data were obtained from the Queensland Cancer Register. The study cohort comprised Queensland residents aged 15 to 39 years who were diagnosed with a first primary invasive cancer between 1982 and 2013. Follow-up on second cancers was available for a minimum of five years to the end of 2018. Standardised incidence ratios (SIRs) were used to approximate the risk of a second primary cancer relative to the general population.

Results: In total, 3,086 second primary cancers were observed among 34,431 eligible AYA patients (9%), equating to an overall SIR of 1.59 (95% CI 1.53-1.64). Melanoma (n=853, 28%) and female breast cancer (n=594, 19%) were the most common types of second primary cancer in the study cohort. Relative risk of all second primary cancers combined among AYA patients was inversely associated with age and was highest within the period immediately following first diagnosis. Patients aged 15-24 at first diagnosis recorded more than four times as many second primary cancers than expected within two years of their first cancer (SIR=4.40, 95% CI 2.83-6.82).

Conclusions: Detailed data on second primary cancers among AYA cancer survivors is important in promoting increased awareness and to inform the development of targeted prevention and surveillance strategies.

Introduction

Cancers among adolescents and young adults (AYA, defined here as ages 15-39 years at diagnosis) span both childhood and adult cancers. AYA cancer survivors may experience a diverse range of challenges compared to other age groups, including unique medical and psychosocial needs, as their diagnosis occurs at a time of life coinciding with critical change and development.(1-3)

A concern facing cancer survivors of any age is the increased risk of being diagnosed with a second primary cancer. However, there is limited literature on second primary cancer specific to survivors of AYA cancer across the full range of cancers. As AYA have a long time to live as survivors, this information is crucial for the affected individuals, and for health services at both the delivery and planning levels.

In this study, our aim was to examine the distribution of second primary cancers diagnosed at any age following a first primary cancer diagnosed between the ages of 15-39 years in Queensland, Australia. We also examined patterns in the relative risk of second cancer by age at first diagnosis and time between first and second diagnosis, as well as assessing specific combinations of first and second cancers.

Materials and Methods

Data

Anonymised records for individual patients were obtained from the population-based Queensland Cancer Register (QCR). As only aggregated de-identified information was used, specific ethics approval was not required for this study. The extract provided by the QCR contained details pertaining to the patients' demographics, diagnosis and death (if relevant). Cancers for the same patient were linked using dummy identifier numbers.

There is no international standard for the definition of the AYA age group. In Australia, AYAs are generally considered to include those aged 15-24 at first diagnosis,(4) whereas the 15-39 age group is favoured in the United States.(5) We decided to use the broader age group in order to capture a sufficient number of cases for the intended analyses, with results presented in three subgroups (15-24, 25-34 and 35-39 years) where possible. This permitted us to determine whether differences exist across the AYA age spectrum, while at the same time allowing for international comparisons.

The study cohort therefore comprised Queensland residents aged 15-39 who were diagnosed with a first primary invasive cancer between 1982 and 2013 and survived for at least six months. Patients were followed from six months after their initial diagnosis until 31st December 2018, date of diagnosis of a second primary invasive cancer, or date of death, whichever came first, thus allowing a potential minimum of five years at risk.

Second primary invasive cancers were determined using the rules published by the International Agency for Research on Cancer (IARC).(6) Under these rules, tumours with different morphologies that occur at the same body site or organ are considered to be distinct.

Two tumours of the same morphology but opposite laterality in paired organs (for example, breast or lungs) are also defined as being separate primaries unless they are known to share a similar origin. As per IARC guidelines,(7) synchronous primary cancers (diagnosed within six months of the first primary cancer) were excluded to minimise detection bias. Third or subsequent primary cancers were also omitted.

Data on the underlying incidence counts of cancer in the general Queensland population up to 76 years old (the maximum obtained age in the study cohort) were also derived from the QCR extract. Estimated resident population information, used as the denominator for calculating incidence rates, was obtained from the Australian Bureau of Statistics.(8) Remoteness of residence (major city, inner regional, outer regional, remote/very remote) and area-based socioeconomic status quintile were assigned according to the Australian Statistical Geography Standard Remoteness Structure(9) and the Index of Relative Socioeconomic Advantage and Disadvantage(10), respectively, based on the place of residence at the time of first diagnosis.

Analyses

Standardised incidence ratios (SIRs) were used to approximate the relative risk of an AYA cancer survivor being diagnosed with a second primary cancer compared to the incidence of cancer in the general population, derived by dividing the observed number of second primary cancers by the expected number. The expected number of second primary cancers was in turn calculated by multiplying the sum of the person-years at risk within the study cohort by the cancer-specific incidence rate experienced by the general Queensland population, matched by sex, 5-year age group and year of diagnosis. Similarly, absolute excess risk was estimated

from the observed minus the expected number of cases divided by person-years at risk and multiplied by 10,000.

Analyses were performed by individual cancer type where numbers allowed. SIRs were also calculated by age group and time between first and second diagnosis, as well as for selected combinations of first and second primary cancers. Differences between SIRs for characteristics of interest were assessed using negative binomial models, where the observed number of second primary cancers was the dependent variable and the offset was the log of the expected number.

All analyses were conducted using Stata software (version 16.1, StataCorp LLC, College Station, Texas). Confidence intervals (CIs) for point estimates were calculated at the 95% level of certainty.

Results

Details of the study cohort (n=34,431) are shown in Table 1. The majority were female (n=19,982, 58%), 18% (n=6,301) were aged 15-24 years at first diagnosis and 89% (n=30,519) had a first primary solid tumour. Median follow-up time for the entire cohort was 14.0 years (interquartile range 7.2-22.5 years).

Melanoma (n=11,773, 34%) was by far the most common type of first primary cancer across all age groups. The distribution of some other cancers, however, varied significantly by age ($p<0.001$). Female breast cancer accounted for less than 1% of all first primary cancers in the 15-24 age bracket (n=57 of 6,301) compared to 19% among those aged 35-39 years (n=2,389 of 12,886). In contrast, blood cancers collectively comprised 20% (n=1,257 of 6,301), 10% (n=1,559 of 15,244) and 9% (n=1,096 of 12,886) of first primary cancers in the 15-24, 25-34 and 35-39 age groups, respectively.

Overall risk of second primary cancers

A total of 3,086 second primary invasive cancers (9% of the study cohort) were diagnosed six or more months after the initial diagnosis, corresponding to an SIR of 1.59 (95% CI 1.53-1.64). The overall cumulative incidence of second primary cancers at 30 years after first diagnosis was 16.3% (95% CI 15.7%-16.9%) and the absolute excess risk was 21.8 per 10,000 patients per year (95% CI 20.4-23.0).

Relative risk of second primary cancer by patient and clinical characteristics

No difference was found in the relative risk of a second primary cancer by sex (p=0.51), both males and females were at increased risk of secondary cancers. There was also no evidence of an ordinal association between the relative risk of a second primary cancer and either remoteness of residence (p=0.54) or area-based socioeconomic status (p=0.61); a secondary cancer was not associated with either remoteness or socioeconomic status – results not shown.

Large differences in the relative risk of any second primary cancer were, however, recorded by age group – Table 1. Patients aged 15-24 years at first diagnosis recorded an SIR of 2.12 (95% CI 1.91-2.35), significantly higher than the relative risk among those aged 35-39 (SIR=1.47, 95% CI 1.39-1.54; p<0.001). For first primary cancers where sufficient cases of second primary cancers were available to stratify by age group (Figure 1), a statistically significant inverse relationship was observed between relative risk and age at first diagnosis following melanoma (p<0.001) or Hodgkin lymphoma (p=0.001), but there wasn't clear evidence of ordinal variation in relative risk by age following colorectal cancer (p=0.89), testicular cancer (p=0.14), thyroid cancer (p=0.56) or non-Hodgkin lymphoma (p=0.31).

First primary blood and lymphatic cancers (SIR=2.06, 95% CI 1.84-2.30) carried a higher relative risk than solid tumours (SIR=1.55, 95% CI 1.49-1.61; p<0.001). Patients with each of the specific first primary cancer types listed in Table 1 (except for brain, lung or kidney cancer) were at a significantly increased risk of second primary cancer compared to the general population.

Changes in relative risk over elapsed time from first diagnosis

Among patients aged 15-24 years, the number of observed second primary cancers was more than four times higher than expected between six months to two years after the first diagnosis (SIR=4.40, 95% CI 2.83-6.82). Similarly, for both the 25-34 and 35-39 age groups, the highest relative risk occurred within the first two years (SIR=2.76 (95% CI 2.19-3.48) and SIR=2.59 (95% CI 2.13-3.16), respectively). For each age group, there was a large decrease ($p<0.001$) in the relative risk of second primary cancers over elapsed follow-up time; nonetheless, the risk of a second cancer among AYA survivors remained significantly higher than cancer incidence rates experienced within the general population, even after 20 or more years (Figure 2).

Type of second primary cancer

Melanoma was the most common type of second primary cancer overall (n=853 of 3086, 28%) followed by female breast cancer (n=594, 19%). Significant differences ($p<0.001$) were found in the distribution of second primary cancer type by age group – Table 2. For example, melanoma accounted for 37% (n=129 of 352) of second primary cancers in the 15-24 age group compared to 23% (n=331 of 1,447) among those aged 35-39 at first diagnosis, with corresponding SIRs of 3.10 (95% CI 2.61-3.68) and 2.08 (95% CI 1.87-2.32), respectively.

Time between the first and second diagnosis also varied significantly ($p<0.001$) according to the type of second primary cancer. The percentage diagnosed within 5 years of the first cancer varied from 1% (n=2 of 166) for second primary prostate cancer to 44% (n=20 of 45) for second primary acute myeloid leukaemia and 47% (n=7 of 15) for Hodgkin lymphoma.

Combinations of first and second cancers

Relative risks for specific types of first and second primary cancers are illustrated in Figure 3 (also see Supplementary Table 1 for further details). The most prominent cancer following AYA female breast cancer was a second primary breast cancer; most of these second tumours had a similar morphology but were in the opposite breast (n=218 of 229, 95%) and around three-quarters (n=166 of 229, 72%) were diagnosed more than 5 years after the first breast cancer. Relative risks following breast cancer were also significantly elevated for second primary lung cancer, gynaecological cancers and melanoma. Among AYA patients with colorectal cancer, the relative risks were highest for a second primary colorectal cancer at a different site and gynaecological cancers. First primary gynaecological cancers in the AYA age group had a highly significant association with second primary lung cancer and head and neck cancer as well as a raised risk for colorectal cancer. The largest relative risks following AYA head and neck cancer were for a second primary head and neck cancer at a different anatomic site or lung cancer, with significantly increased relative risks also recorded for second primary colorectal cancer and melanoma. AYA patients with either Hodgkin or non-Hodgkin lymphoma combined had very high SIRs for second primary non-Hodgkin lymphoma, thyroid cancer, and lung cancer, as well as an elevated risk for second primary head and neck cancers, gynaecological cancers, breast cancer, colorectal cancer and melanoma. Following a first primary AYA melanoma, the risk of a second primary melanoma was four times higher than would otherwise be expected, and risks for second primary brain cancer, thyroid cancer and prostate cancer were also significantly raised. Patients with testicular cancer had a very high relative risk of being diagnosed with a second primary testicular cancer on the opposite side. There was an association between AYA thyroid cancer patients and second primary melanoma.

Discussion

In this study we have detailed the increased risk of cancer experienced by survivors of AYA cancer compared to incidence rates in the general population. Our results add to the limited existing literature on the full spectrum of second primary cancers following any first primary AYA cancer, particularly in regard to the period within five years following the initial diagnosis.

Published population-based estimates of the overall relative risk for second primary cancers following AYA cancer from Italy(11) and the United States(12) were 1.58 and 1.60, respectively; both very similar to the overall SIR of 1.59 reported here. Lee *et al*(12) calculated a 30-year cumulative incidence of 13.9% for second primary cancers following AYA cancer based on SEER data, slightly lower than the 30-year cumulative incidence of 16.3% in our cohort. Interpreting such comparisons is complex, however, because of differing methods; for instance, the previous studies only considered second primary cancers diagnosed five or more years (11, 12) after first diagnosis.
Another distinction is the much higher incidence of melanoma in Queensland, accounting for 28% of all second cancers in contrast to only 9% in the SEER cohort.(12)

One of the main factors driving the increased risk of second cancers is the potentially hazardous effects of adjuvant treatment for the initial cancer, typically with a latency period of many years. A literature review conducted by Bukowinski et. al.(13) concluded that some AYA cancer patients tend to have an inferior response to treatment and/or adverse disease biology, necessitating a stronger regimen of chemotherapy and/or radiotherapy. Intensification of treatment in turn leads to an increased risk of second primary cancer. Some prominent examples of second primary cancers in younger cancer patients linked to

radiotherapy include thyroid or breast cancer following lymphoma(14, 15) and lung cancer following breast cancer.(16, 17)

The results presented here showed that relative risk of second primary cancer was highest within the first two years following initial diagnosis for all AYA age groups, with a greater than fourfold excess risk during this period among those aged 15-24. A similar association has been reported among childhood cancer survivors (ages 0-14) in Australia, for whom the SIR was also found to be highest in the interval immediately following the initial cancer.(18) More intensive medical watchfulness during the period following cancer diagnosis may have contributed to this result, although synchronous cancers were removed from the analysis. Another possible explanation is that the elevated risk of second cancers while patients are still undergoing active treatment may be indicative of genetic factors rather than the effects of chemotherapy and radiotherapy.

An apparent gradient in relative risk by age group at first diagnosis (i.e. the cancer risk in AYA cancer survivors compared to that in the same age group in the general population) was noted in our cohort. This is likely to reflect lower underlying rates of cancer at the population level amongst the younger age groups. We found, however, that the pattern of relative risk by age varied when stratified by type of first primary cancer. It is possible that variations in the effects of treatment by age at first diagnosis may also contribute.(13)

Aside from second cancers linked to the late effects of treatment for the first cancer, profiling cancers which have a high risk of occurring together is useful for identifying possible shared causes.(19, 20) The higher than expected number of second primary cancers among AYA cancer survivors may be attributed to patient characteristics such as genetics; lifestyle factors

including smoking, alcohol consumption and obesity; environmental and occupational hazards; or some combination of these and other possible causes.(7) In the current study, relative risks tended to be highest for combinations of first and second primary cancers at the same or related sites. This might be expected if causal factors are similar; for example, multiple cutaneous melanomas due to sun exposure in those with susceptible skin types and pigmentation.(21) Treatment for AYA gynaecological cancers typically involves removal of some or all of the reproductive organs,(22) which would explain why there was not an elevated risk of second cancers at these sites. We also observed a high risk of lung cancer following female breast cancer, gynaecological cancers, head and neck cancer and lymphoma, in agreement with results from a recent UK study,(23) and consistent with multiple reports of an increased prevalence of smoking among AYA cancer survivors compared to their peers.(24-26) Some of the other combinations of first and second primary cancers occurring in excess at a young age that were identified here (eg. colorectal and gynaecological cancer) may be linked to inherited predisposition syndromes such as Lynch Syndrome.(7)

The study was based on administrative data that was recorded independently, hence removing the potential for recall bias among patients. One important limitation is that subsequent cancers diagnosed interstate or overseas for the same patient are not routinely notified to the Queensland Cancer Register. This is likely to have more of an impact on the AYA cohort than for older adults due to the generally higher mobility of this age group, leading to an underestimate of relative risk due to a lower number of observed second primary cancers. However, it was not possible to measure the effect that interstate/overseas migration may have on the estimates presented here. A national study is recommended, as it would have the advantage of not only increasing the number of cases available, but would also overcome the

issue of patients moving between states. The extract from the QCR did not contain clinical information, so it was not possible to identify which patients were diagnosed with a second primary cancer whilst still under active treatment. Data on stage were also not available for most cancers, so we were unable to assess whether second cancers were diagnosed at an earlier or later stage.

While it would be of interest to investigate whether relative risk changed according to the decade of diagnosis and treatment, it was not feasible to examine this issue because follow-up would need to be truncated to allow for consistency when comparing estimates. As stated earlier, many treatment-related second cancers have longer latency periods, making evaluation of any changes in relative risk within a few years of diagnosis less meaningful from the perspective of treatment evolution.

Quantifying and characterising the likelihood of second malignancies within this younger cohort of cancer patients has important implications for increased awareness and surveillance leading to early detection as well as the development of prevention strategies.(27, 28) The fact that relative risks were highest for second cancers occurring at either a related anatomic site or second primary lung cancers raises the possibility of implementing prevention strategies in situations where there might be a modifiable lifestyle or environmental risk factor. Our results also emphasise the importance of vigilance in the detection of second primary cancers from soon after first diagnosis, given that this is the time during which relative risk is greatest.

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Data access statement: The data used in this study may be requested directly from the Queensland Cancer Register (subject to obtaining the necessary ethics approvals).

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Table 1: Numbers of second primary cancers and standardised incidence ratios following a first primary AYA cancer by selected patient characteristics, Queensland, 1982-2018

Characteristic	Number of first primary cancers[a]	Number of second primary cancers	Standardised incidence ratio (95%CI)
Total	34,431	3,086	1.59 (1.53-1.64)
Sex			
Males	14,449	1,188	1.61 (1.52-1.70)
Females	19,982	1,898	1.57 (1.50-1.64)
Age group at first diagnosis			
15-24	6,301	352	2.12 (1.91-2.35)
25-34	15,244	1,287	1.62 (1.54-1.72)
35-39	12,886	1,447	1.47 (1.39-1.54)
Type of first cancer			
Solid cancers			
Brain cancer	1,021	26	1.10 (0.75-1.62)
Breast cancer (females)	3,841	447	2.03 (1.85-2.22)
Colorectal cancer	1,854	125	1.42 (1.19-1.69)
Gynaecological cancers	3,019	276	1.23 (1.09-1.38)
Head and neck cancers	1,503	152	1.48 (1.27-1.74)
Kidney cancer	409	27	1.28 (0.88-1.86)
Lung cancer	324	18	1.51 (0.95-2.39)
Melanoma	11,773	1,249	1.61 (1.53-1.71)
Testicular cancer	2,193	162	1.50 (1.29-1.75)
Thyroid cancer	2,111	141	1.27 (1.07-1.49)
Other solid cancers	2,471	158	1.42 (1.22-1.66)
Blood/lymphatic cancers			
Hodgkin lymphoma	1,140	103	2.31 (1.90-2.80)
Lymphoid leukaemia	411	21	2.02 (1.32-3.10)
Myeloid leukaemia	657	35	1.92 (1.38-2.68)
Non-Hodgkin lymphoma	1,168	104	2.06 (1.70-2.50)
Other blood/lymphatic cancers	536	42	1.71 (1.26-2.31)

Note: a. First primary cancers were diagnosed between 1982 and 2013 for patients who survived for a minimum of six months.

Table 2: Most common types of second primary cancers diagnosed among AYA cancer survivors by age at first diagnosis, Australia, 1982-2018

Type of second primary cancer	n	%	Standardised incidence ratio[a] (95%CI)
15-39 years old at first diagnosis[b]			
Melanoma	853	27.6	2.40 (2.25-2.57)
Female breast cancer	594	19.3	1.40 (1.29-1.52)
Colorectal cancer	202	6.6	1.23 (1.07-1.41)
Lung cancer	175	5.7	1.69 (1.46-1.96)
Prostate cancer	166	5.4	1.13 (0.97-1.32)
TOTAL[c]	**3,086**	**100.0**	**1.59 (1.53-1.64)**
15-24 years old at first diagnosis[b]			
Melanoma	129	36.7	3.10 (2.61-3.68)
Female breast cancer	54	15.3	1.82 (1.39-2.37)
Testicular cancer	19	5.4	2.81 (1.86-4.56)
Thyroid cancer	18	5.1	1.75 (1.10-2.77)
Head and neck cancers	16	4.6	2.36 (1.44-3.85)
TOTAL[c]	**352**	**100.0**	**2.12 (1.91-2.35)**
25-34 years old at first diagnosis[b]			
Melanoma	393	30.5	2.55 (2.31-2.81)
Female breast cancer	224	17.4	1.31 (1.15-1.49)
Colorectal cancer	80	6.2	1.24 (0.99-1.55)
Lung cancer	65	5.1	1.73 (1.36-2.20)
Gynaecological cancers	61	4.7	1.14 (0.89-1.46)
TOTAL[c]	**1,287**	**100.0**	**1.62 (1.54-1.72)**
35-39 years old at first diagnosis[b]			
Melanoma	331	22.9	2.08 (1.87-2.32)
Female breast cancer	316	21.8	1.42 (1.27-1.59)
Colorectal cancer	108	7.5	1.23 (1.01-1.48)
Prostate cancer	105	7.3	1.18 (0.97-1.43)
Lung cancer	96	6.6	1.56 (1.28-1.90)
TOTAL[c]	**1,447**	**100.0**	**1.47 (1.39-1.54)**

Note: a. Standardised incidence ratios were calculated following any first primary cancer within that age group. b. First primary cancers were diagnosed between 1982 and 2013 for patients who survived for a minimum of six months. c. Five most common cancers only within each age group are shown do not add to total.

Figure legends

Figure 1: Standardised incidence ratios for all second primary cancers combined by age group and type of first primary AYA cancer, Australia, 1982-2018.
Note: First primary cancers were diagnosed between 1982 and 2013 for patients who survived for a minimum of six months. Y-axis is on the log scale.

Figure 2: Standardised incidence ratios for second primary cancer by age group and time from first diagnosis following AYA cancer, Australia, 1982-2018.
Note: First primary cancers were diagnosed between 1982 and 2013 for patients who survived for a minimum of six months. Y-axis is on the log scale.

Figure 3: Standardised incidence ratios for type of second primary cancer following first primary AYA cancer, Australia, 1982-2018.
Notes: Second primary cancers with a minimum of 10 observed cases are shown. First primary cancers were diagnosed between 1982 and 2013 for patients who survived for a minimum of six months. Y-axis is on the log scale. NHL – non-Hodgkin lymphoma.

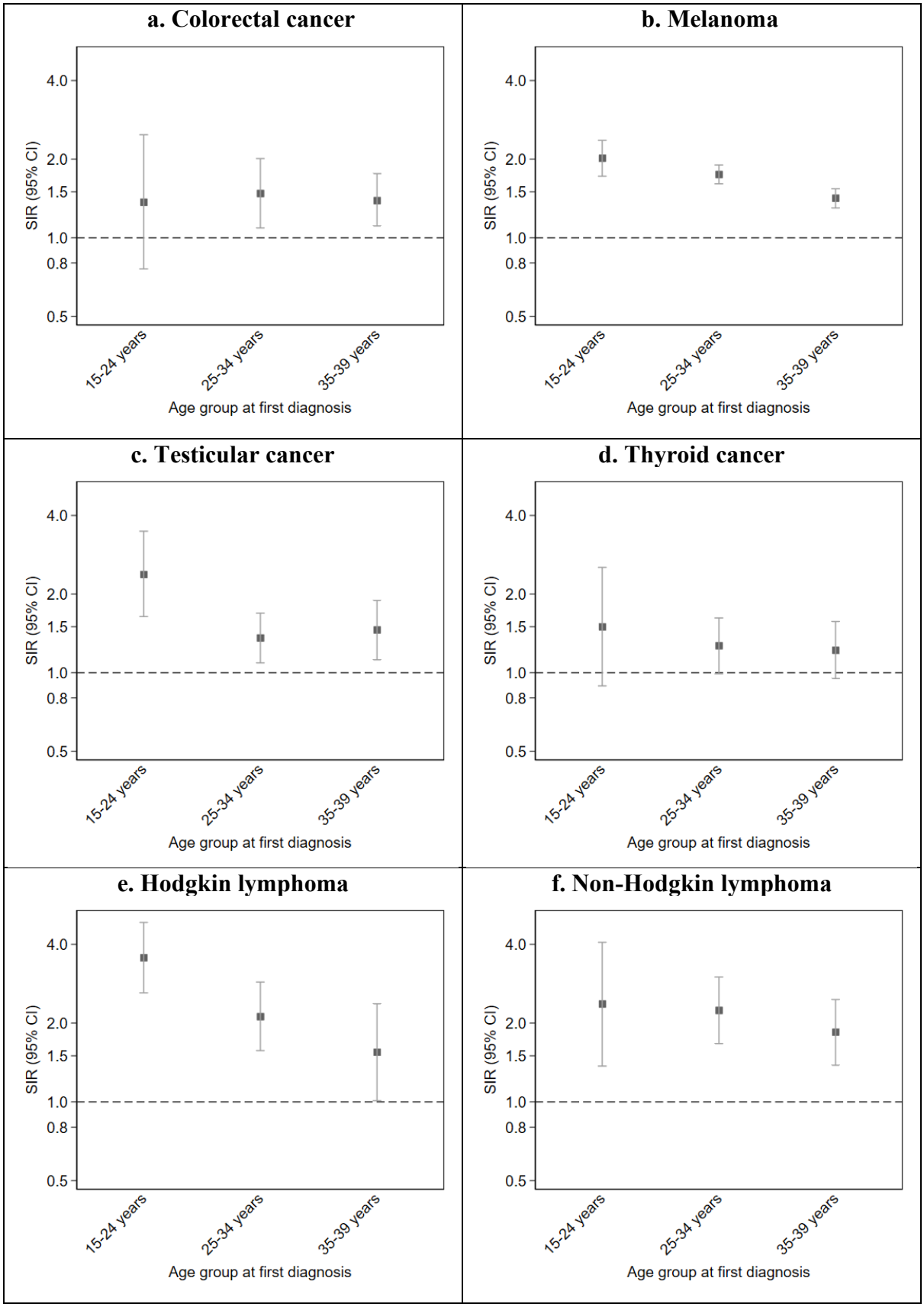
a. Colorectal cancer
b. Melanoma
c. Testicular cancer
d. Thyroid cancer
e. Hodgkin lymphoma
f. Non-Hodgkin lymphoma
SIR (95% CI)
4.0
2.0
1.5
1.0
0.8
0.5
15-24 years
25-34 years
35-39 years
Age group at first diagnosis

Figure 1.

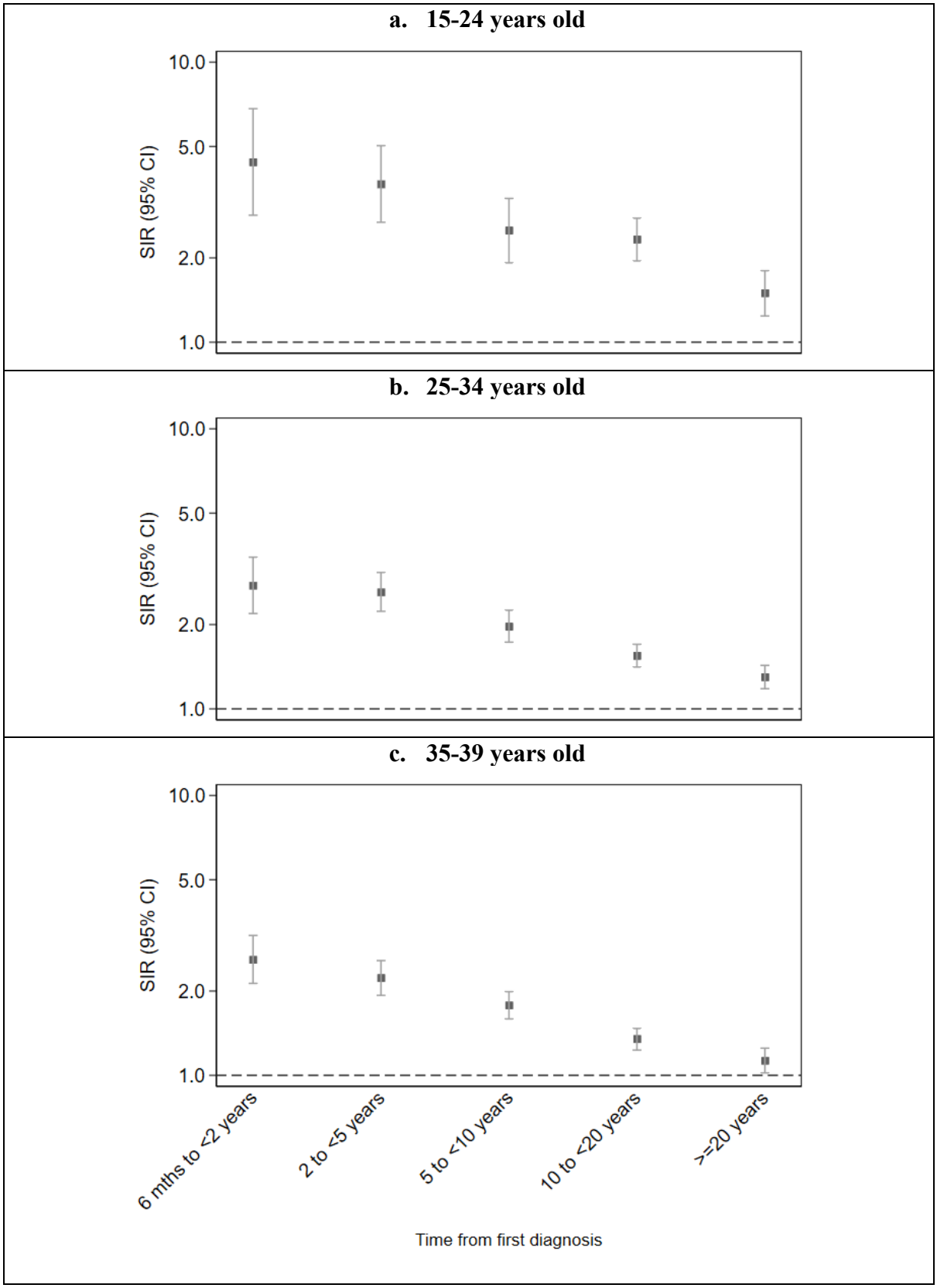
a. 15-24 years old
b. 25-34 years old
c. 35-39 years old
SIR (95% CI)
10.0
5.0
2.0
1.0
6 mths to <2 years
2 to <5 years
5 to <10 years
10 to <20 years
>=20 years
Time from first diagnosis

Figure 2

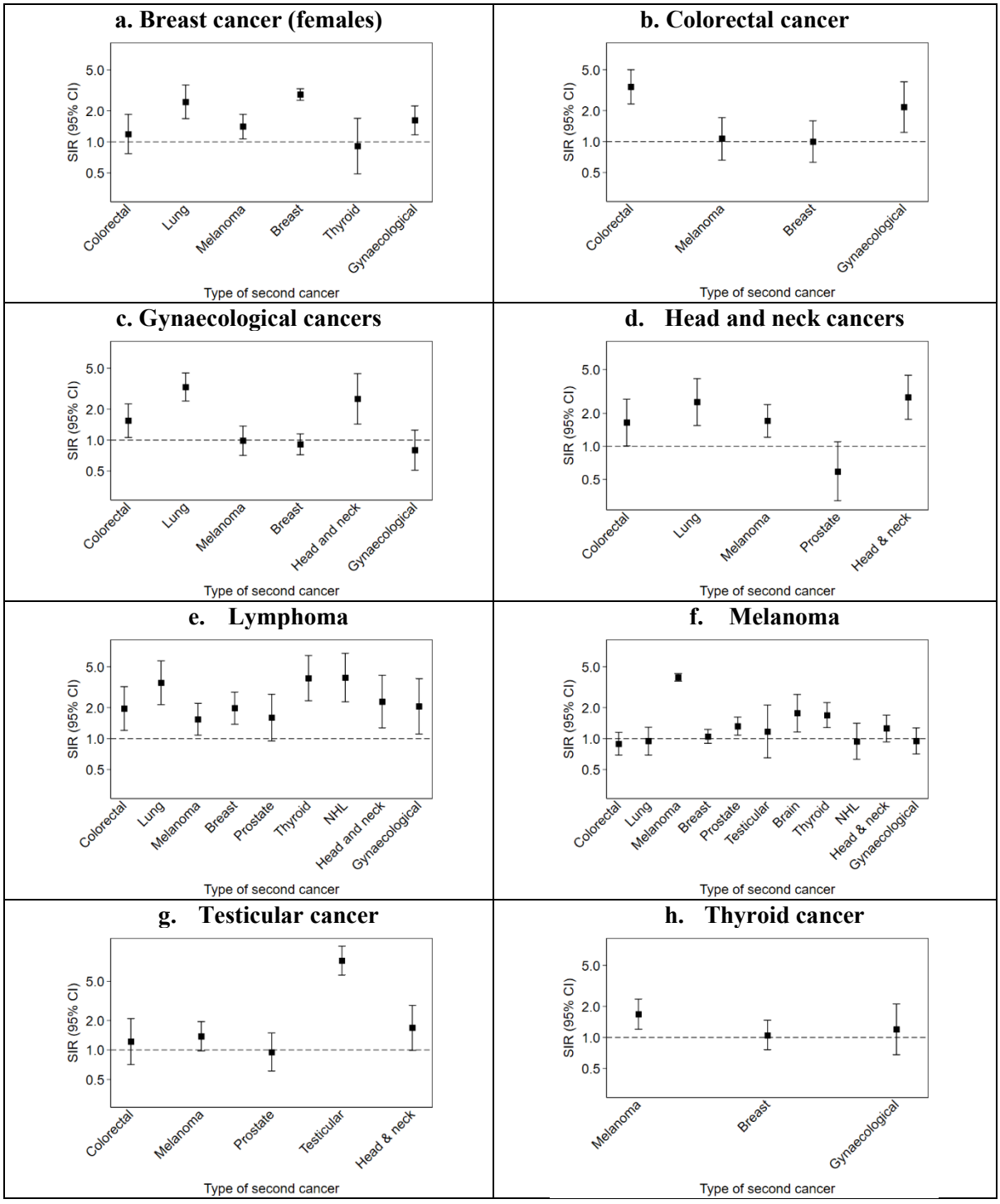
a. Breast cancer (females)
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Lung
Melanoma
Breast
Thyroid
Gynaecological
Type of second cancer
b. Colorectal cancer
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Melanoma
Breast
Gynaecological
Type of second cancer
c. Gynaecological cancers
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Lung
Melanoma
Breast
Head and neck
Gynaecological
Type of second cancer
d. Head and neck cancers
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Lung
Melanoma
Prostate
Head & neck
Type of second cancer
e. Lymphoma
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Lung
Melanoma
Breast
Prostate
Thyroid
NHL
Head and neck
Gynaecological
Type of second cancer
f. Melanoma
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Lung
Melanoma
Breast
Prostate
Testicular
Brain
Thyroid
NHL
Head & neck
Gynaecological
Type of second cancer
g. Testicular cancer
SIR (95% CI)
5.0
2.0
1.0
0.5
Colorectal
Melanoma
Prostate
Testicular
Head & neck
Type of second cancer
h. Thyroid cancer
SIR (95% CI)
5.0
2.0
1.0
0.5
Melanoma
Breast
Gynaecological
Type of second cancer

Figure 3.