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**Multiple primary cancers among colorectal cancer survivors in Queensland, Australia, 1996-2007**

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**Abstract**

**Purpose:** To quantify the demographic and clinical factors associated with an increased risk of multiple primary cancers (MPCs) among colorectal cancer survivors.

**Methods:** Standardised incidence ratios for MPCs were calculated for residents of Queensland, Australia, who were diagnosed with a first primary colorectal cancer between 1996 and 2005 and survived for at least 2 months. Relative risk ratios were calculated for all MPCs combined and selected individual sites using multivariate Poisson models.

**Results:** A total of 1,615 MPCs were observed among 15,755 study patients. The cohort had a significant excess risk of developing subsequent colorectal (SIR = 1.47, 95% CI 1.30-1.66) or non-colorectal (SIR = 1.24, 95% CI 1.18-1.31) cancers relative to the incidence of cancer in the general population. Age at initial diagnosis, follow-up time, initial colorectal subsite and surgical treatment were independently associated ($p < 0.01$) with the overall risk for developing MPCs after adjustment. The relative risk ratio was 1.23 (95% CI 1.07-1.41) for those aged 20-59 years compared to the 70-79 age-group and 0.82 (95% CI 0.72-0.92) for 1-5 years follow-up relative to the first year. The likelihood of being diagnosed with a MPC was 33% higher (95% CI 1.12-1.56) for surgically treated patients and 45% higher (95% CI 1.29-1.64) after proximal colon cancers relative to rectal cancer.

**Conclusions** While these population-based results do not incorporate all possible risk factors, they form an important foundation from which to further investigate the etiological causes that result in the development of MPCs among colorectal cancer survivors.

## INTRODUCTION

Colorectal cancer (CRC) is a major public health problem,(1) particularly in more developed countries where it is the most commonly diagnosed invasive cancer.(2) With increasing incidence and improving survival, the number of CRC survivors living after their diagnosis of cancer is continuing to rise.(3)

One of the challenges faced by the growing number of survivors is the possibility of being diagnosed with a subsequent tumour,(4)with its associated implications in terms of poorer quality of life(5) and decreased long-term survival.(6) Several Australian and international studies in recent years have examined the risk of developing new primary cancers following an initial CRC diagnosis.(7-12) The focus of most of these studies has been on identifying which cancer types were more likely to occur after the initial CRC, with inconsistent results. Apart from generally higher risks reported among females and those diagnosed at younger ages,(8, 9, 12) little data is available describing which patient and clinical characteristics are associated with increased risk of multiple primary cancers (MPCs).

Using a large population-based dataset of Queensland residents diagnosed with a first primary CRC, the aims of this study were to quantify the risk of subsequent cancers among CRC survivors relative to the general population, and to investigate the demographic and clinical factors that are independently associated with increased risk. These data will assist clinicians and cancer support personnel in identifying those patients who could most benefit from heightened medical surveillance.

## MATERIALS AND METHODS

Ethical approval to conduct this study was obtained from the University of Queensland Social and Behavioural Sciences Ethical Review Committee. Queensland Health gave legislative consent to access routinely collected population-based cancer incidence data in Queensland and to link this with the Queensland Hospital Admitted Patient Data Collection.(13)

### *Study Cohort*

The initial extract comprised all patients diagnosed with an invasive CRC (ICD-O-3 codes C18 to C20, C21.8 between January 1, 1996 and December 31, 2005 (inclusive). Our cohort was then restricted to those aged 20-79 at diagnosis since CRC is very rare among younger individuals and there is evidence of under-reporting of second cancers among elderly patients due to increased co-morbidities and shortened life expectancies.(11, 14) Other recent studies have also used a similar cut-off.(11, 15, 16) Cases were extracted from the Queensland Cancer Registry, a state-wide population-based registry to which all confirmed invasive cancers diagnosed among Queensland residents must be legally reported.(17) The final cohort was followed up to 31 December 2007, a minimum of 2 years from the time of initial diagnosis for each patient who did not die prior to the end date.

Information on subsequent diagnoses of invasive primary cancers was also obtained from the Queensland Cancer Registry. The IARC rules for classifying MPCs were followed,(18) which define each MPC as an invasive cancer that originated in a separate anatomical site or one that was histologically different from the first (index) tumour. Cancers which occurred at a different subsite of the colon (C18) or skin (C44) were treated as separate primaries.(18)

To reduce the impact of potential surveillance bias, new malignancies diagnosed within the first 2 months of follow-up were excluded.(19) Persons were also excluded if they had another invasive cancer prior to their first CRC diagnosis.

*Treatment and Co-morbidities*

A deterministic linkage(20) between the cancer registry and hospital admissions databases was used to ascertain whether study patients underwent local excision (810, 908, 914, 933), resection (913, 915, 934-936) or other surgical procedures (897, 899, 917-918, 984-985) for CRC within 2 years of diagnosis. Hospital co-morbidities are defined as a condition that is either co-existing with the principal diagnosis or arose during the episode of care and influences a patients clinical management in-hospital.(13) ICD-10-AM diagnostic codes from hospital records were used to identify whether CRC patients were diagnosed with either of the two most frequent co-morbidities: heart disease (I50) and diabetes (E10-E14).

*Colorectal Cancer Staging*

As has been described previously,(21, 22) information extracted from pathology forms was used to determine CRC stage at diagnosis according to the TNM system.(23) Localized cases (Stages I-II) were grouped together as “early stage” while regional and distant tumours (Stages III-IV) were categorized as “advanced stage”(24) to allow sufficient numbers when modelling.

*Statistical Analysis*

Time at risk was accumulated from two months after diagnosis of the index CRC to the diagnosis of each metachronous cancer (more than 2 months after initial diagnosis), death, or the study endpoint, whichever occurred first. Separate records were generated for the same person if they had two or more MPCs at different sites (0.6% of cohort). Each MPC was analysed as if it was the first multiple primary with no regard for any intervening cancer diagnoses and associated treatment. Other studies have used a similar approach. (7, 9, 11).

Five-year age and sex-specific incidence rates among the general Queensland population were multiplied by the corresponding aggregated persons-years of risk to estimate the expected numbers of subsequent malignancies by cancer type. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected numbers of cases, thus providing an estimate of the risk of a CRC survivor developing another primary cancer relative to the incidence of cancer among the general population. A Poisson distribution was assumed for the observed

cases when calculating the 95% confidence intervals (CIs), and SIR estimates were deemed statistically significant ($p<0.05$) if the resultant CI did not include 1.00.(19)

Stratified analyses by sex, age group and follow-up interval were used to estimate SIRs for cancer sites with at least 20 observed cases in total. Risk patterns for developing MPCs by anatomic location defined as proximal (C180 to C184), distal (C185-C187), unspecified colon (C188-C189) or rectum (C19-C20, C218)(25) were also assessed.

Multivariate Poisson regression with a clustering factor to account for multiple cancers in the same individual was used to estimate relative risk ratios (RRRs) with 95% CIs, for all MPC sites combined and for the seven most common sites. The dependent variable was the observed number of MPCs, with the log of the expected number of subsequent cancers used as the offset variable. Models were adjusted for potential confounding by sex, age at initial diagnosis, follow-up interval, index CRC site, stage, surgery and diabetes. Heart disease was not included in final models since it was not significant at the bivariate level.

All analyses were performed with Stata version 11.2 (StataCorp, TX).

## RESULTS

### *Study Cohort*

The initial cohort included all CRC patients in Queensland diagnosed between 1996 and 2005 (n=22,402). We excluded individuals aged below 20 (n=15, 0.1%) or older than 79 years (n=4,211, 18.8%) at CRC diagnosis, those who died within 2 months of diagnosis (n=904, 4.0%) and those who were diagnosed with another invasive cancer prior to their first CRC diagnosis (n=1,517, 6.8%). This left 15,755 survivors of first primary CRC (70.3%) who were eligible for inclusion in the study.

More than half (57.7%) of the final cohort were male, the mean age at diagnosis was 64 years and there were 32.8% proximal colon, 25.4% distal colon, 5.4% unspecified colon and 36.4% rectal cancer cases. The index CRC stage distribution was early (48.8%), advanced (36.1%) and unknown (15.1%).

### *Characteristics of Multiple Primary Cancers*

A total of 1,615 MPCs were observed during the 69,704 years of follow-up (median = 4.2 years per person; interquartile range = 2.2 to 7.3 years) that were accumulated for the study cohort. The median time from initial diagnosis to development of a MPC was 37 months, with around one-fifth (21.5%) being diagnosed within 1 year. Thirty per cent of all MPCs diagnosed within the first year were CRCs. Over the entire study CRC was the most frequent type of MPC (n=273, 16.9%), followed by prostate cancer (n=265, 16.4%), lung cancer (n=202, 12.5%) and melanoma (n=168, 10.4%).

### *Relative Risk of Multiple Primary Cancers after Colorectal Cancer*

Colorectal cancer survivors in our cohort had a significant excess risk of developing subsequent colorectal (SIR = 1.47, 95% CI 1.30-1.66) or non-colorectal cancers (SIR = 1.24, 95% CI 1.18-1.31). Risks were significantly higher for both male and female patients compared to the general age-matched Queensland population, and remained significant even after second primary CRCs were excluded (Table 1). Significantly elevated relative risks were observed for cancers of the colon, rectum (females only), prostate, lung, female breast, uterus, kidney, stomach, small intestine, melanoma (males only), bladder (males only) and myelodysplastic diseases. In contrast, there were significantly fewer rectal cancers among males and unknown cancers among females than were expected.

Across all age groups, the study cohort had a higher risk of MPCs than the corresponding general population, although there was some suggestion that the risk estimates tended to decrease with increasing age at initial diagnosis (Table 2). Cancers of the colon and lung were the only sites which exhibited a significantly increased risk in all three age groups, while the risk of cancers of the small intestine was around 5 times higher than expected for those aged 60 years and over and the risk of uterine cancer was trebled among female CRC survivors aged 20-59 years although absolute numbers are very small.

The overall SIRs were significantly high across all follow-up intervals, varying from 1.51 (95% CI 1.35-1.67) during the first year of follow-up to 1.23 (95% CI 1.14-1.31) between 1-5 years after the initial diagnosis (Table 3). The risk of another primary CRC was almost three times higher for our cohort compared to the general population within the first year. Elevated risks for colon cancers were significant for up to five years of follow-up but an increased risk for rectal cancers was limited to the first year, and the observed number of subsequent rectal cancers was actually significantly lower than expected after 5 years follow-up. A higher risk of lung cancer was seen throughout all follow-up periods while the risks of melanoma, prostate and stomach cancers only became significantly higher after 5 years.

*Multivariate Poisson Modelling*

Multivariate analysis (Table 4) showed that younger CRC patients had a significantly higher relative risk of a MPC than older patients. Relative risks for all MPCs combined were also significantly higher in the first year after diagnosis, for index colon cancers and for surgically treated patients. There was no evidence of a disparate risk of MPCs with the index CRC stage, even when stage was considered at a finer level (results not shown), nor did the surgical effect differ by initial CRC site (results not shown). Also no association with diabetes was found.

The models by individual cancer types revealed that the adjusted relative risk for multiple CRC primaries was higher for females than males whereas there were no statistically significant gender-related differences for other MPCs (Table 5). Survivors aged 20-59 years at first diagnosis had a higher relative risk of being diagnosed with another CRC compared to those aged 70-79 years. Relative risks were also significantly lower for follow-up of more than 1 year compared to the first year for both secondary CRC and kidney cancers. However, women had a higher relative risk of developing breast cancer after the first year. Both proximal and distal colon cancer

survivors had significantly elevated relative risks for subsequent CRC or prostate cancer compared to rectal cancer patients. The increased risk after surgery remained significant when multiple primary CRCs were excluded (Table 4), but there was no significant association for any individual MPC type except CRC (Table 5).

When looking at colon cancers separately, the overall relative risk estimate for MPCs after proximal colon cancer was significantly elevated compared to distal colon cancer survivors (RRR = 1.18; 95% CI 1.04-1.31, p=0.031). However there were no differences in the risk of individual types of MPCs by initial colon cancer location (results not shown).

## DISCUSSION

Our results demonstrate that CRC survivors faced a 28% higher risk of being diagnosed with a subsequent cancer compared to the general Australian population. While other Australian(10, 26, 27) and international studies(7-9, 11, 14) have documented elevated risks of MPCs for CRC survivors, especially at the same site, such studies have only presented crude risks for subsequent cancers without controlling for potential confounders. Literature on adjusted relative risk estimates for MPCs is sparse and, with the exception of a recent breast cancer study,(28) tend to only quantify the risks of treatment-induced cancers.(15, 16, 29) To our knowledge no study has previously reported adjusted relative risk estimates for MPCs in Australia.

Colorectal cancer survivors are at increased risk of developing additional cancers due to a variety of reasons, including genetic susceptibility,(30) molecular phenotypes,(31) shared lifestyle or environmental exposures,(9, 19) treatment for the initial cancer,(16) or a combination of these effects.(4) Recent studies suggest that the majority of subsequent cancers may not be explained simply by receiving radiotherapy for the first primary(16) and highlight the influence of patient characteristics(32) on individual variability.

We used multivariate Poisson modelling incorporating expected rates of cancer in the age and sex-matched general population and controlled for potential confounding to identify subgroups within our cohort of CRC survivors who were most at risk of MPCs. This study provides quantitative evidence that the relative risk of developing another cancer was independently associated with the age at first onset, follow-up interval, index CRC type and surgical treatment.

The adjusted relative risk estimates for MPCs over all sites combined decreased progressively with increasing age at initial diagnosis. Several previous studies have identified early age at first diagnosis as a risk factor for subsequent cancers using narrower age groups (30-49, 50-69, above 70) in stratified analysis.(14, 26, 27) While our current study combined patients aged less than 60 years in one group to ensure stable estimates, we showed that the association with age was independent of the other factors. The effect of age at diagnosis can be at least partially explained by genetic conditions predisposing a subset of younger CRC survivors to a range of early-

onset tumours.(30) It is thought that the reduced risk for older individuals may also be influenced by possible under-ascertainment of MPCs due to competing risks from increased co-morbidities and shortened life expectancy.(9, 19)

We found that the risk of MPCs was generally higher soon after the index CRC; the only significant exception being that the risks for female breast cancer increased with longer follow up intervals. Heightened medical surveillance during initial follow-up(9, 14) probably explains at least some of the early excess. This is consistent with the noticeable shift to earlier stage for additional CRCs diagnosed within the first year especially after surgery (results not shown). The temporal patterns for subsequent breast cancer risk may reflect its relatively long pre-clinical phase and the cumulative effect of hormonal and other exposures on disease onset.(33, 34) Reduced risks of subsequent rectal cancers among rectal cancer survivors (SIR 0.57; 95% CI 0.30-0.98) may be attributed to the rectum being routinely removed during surgery for the first cancer.(35)

Statistically significant relative risks for our cohort were also largely confined to colon cancer survivors, with the risk after rectal cancer for non-colorectal cancers generally being the same as or lower than for the general population, although this effect was not consistent by sex (see below). The persistence of this effect after multivariate analysis highlights the potential importance of anatomic location in determining the risk of MPCs. Reasons for this are unclear but may be related to underlying molecular heterogeneity of different CRC subtypes.(36) Differences in the influence of unmeasured shared lifestyle and behavioural factors (notably obesity, smoking and physical activity) as well as adjuvant treatments between colon and rectal cancer patients are also likely.

Furthermore, the overall risk of MPCs was highest after proximal colon cancer. As far as we are aware, such an independent association has not been previously reported. Proximal tumours are increasingly thought to be a distinct biological entity from other CRC subtypes,(37) hence it could be speculated that these differences may influence the site-specific risk of subsequent MPCs. Other likely explanations include variations in surveillance or treatment by tumour location or differential associations with unmeasured lifestyle factors as mentioned above. We lacked the necessary data to further explore these issues.

Previous studies on MPC risks among CRC patients have either been restricted to surgically treated patients only(11, 27) or have not reported the impact of surgery on estimates.(8, 14) Surgical treatment for CRC was found to be an independent factor for increased overall risk of MPCs within our cohort, even when multiple primary CRCs were excluded. While there is no obvious explanation for this effect, evidence-based guidelines currently recommend increased medical surveillance following CRC-related surgery,(38) which may increase the likelihood of MPCs being diagnosed. It is also possible that surgery is a proxy for other unmeasured factors. Nor can we exclude the prospect that unknown factors associated with surgical treatment may influence the risk of MPCs causing residual confounding. Even so, the observed effect may indicate an as yet unidentified difference among CRC survivors according to whether they underwent surgery. For example, increased risks

may be associated with postoperative inflammatory response and host immunosuppression(39, 40) given the well-established link between these factors and increased risk of CRC.(41)

Female gender also emerged as an independent risk factor for multiple CRCs in multivariate modelling. Moreover the risk of additional rectal cancers following colon cancer (results not shown) was significantly higher than expected among females whereas it was reduced significantly among males. The greater risks for females probably reflect previously reported disparities by gender in pathways of colorectal carcinogenesis.(42) No gender difference in overall risk for MPCs or any other individual site was evident after adjustment, suggesting that residual confounding may have impacted reported differences by sex in previous stratified analyses.(14, 26)

We found an excess of lung cancer over all age groups, follow-up periods and index CRC sites. Published evidence for an association between lung cancer and CRC is inconsistent, with some studies reporting increased risks only after rectal cancer(14) whereas others found no evidence of a significant excess or even decreased risks.(9, 26). While reasons for these differences are unclear, they may reflect, in part, differences in tobacco exposure(14) as long-term smoking has been associated with both lung and colorectal cancers.(43)

Increased risks for cancers of the digestive tract, kidney, bladder, breast and uterus probably reflect shared genetic, hormonal, dietary and other lifestyle factors.(9, 14, 43) Dietary factors(44)and similar genetic mutations(45) have also been implicated as risk factors for both colon and prostate cancers. By contrast, shared causal agents are improbable for some cancer pairs, notably CRC and melanoma; rather, this association is more likely to be due to increased medical surveillance especially during the early follow-up period. An association between CRC and melanoma has been previously reported in studies from Australia(12, 26), which has the highest global incidence rates of melanoma,(2) but not in international studies.(9, 14)

*Strengths & Limitations*

The use of multivariate Poisson models to quantify the independent effects of potential demographic and clinical risk factors provides important and novel information, especially in the context of delivering benchmark information for future studies. These first findings in an Australian context add important data from a unique environment, thus adding to the international body of evidence regarding risk factors for secondary cancers among CRC patients. While some of the variation compared to other studies could be explained by differential surveillance patterns, particularly for those treated with surgery, highlighting these independent associations allows for informed speculation about possible mechanisms thereby generating hypotheses for further exploration. This provides an important platform and motivation to guide future studies.

A major strength of cohort studies based on data from population-based registries is the larger sample size compared to most studies that rely on active respondent participation. These greater numbers allow for more

detailed exploration of risks for rarer MPCs. However this advantage is offset by the limited availability of data on a range of plausible exposures in the etiology of various cancers compared to when patients are contacted, particularly in regard to lifestyle behaviours. Detailed data on issues such as smoking, alcohol consumption, diet and physical activity is typically obtained by extensive follow up of individual patients through questionnaires and medical records,(46) but even then selection bias, incomplete data and limited statistical power due to a smaller sample size can prove to be problematic.

A more complete picture can be obtained through the integration of these complementary methodologies to comprehensively investigate the etiology of multiple cancers.(4, 46) It is hoped that the results of this study, while adding important and novel information regarding the independent contribution of various risk factors, should therefore not be viewed in isolation, but as a foundation and motivation to develop more detailed investigations into lifestyle and genetic factors that may explain additional variations in the risk of MPCs among CRC survivors. This is especially important given the current lack of such studies.

The strengths of this study include the population based nature of the cohort and the use of registry data that was collected independently of our hypotheses. Multivariate analyses allowed us to control for the available confounders such as age at first onset, follow-up period and CRC stage. Linkage to a hospital administrative database provided information on surgical treatment and selected co-morbidities, although some misclassification may arise since only admissions within Queensland were included and missing treatment information (13% of the cohort) could be related to the notification process, data matching procedure or surgery outside the coverage area.

The use of registry based data restricted our ability to quantify the independent effects of several additional risk factors given the Queensland Cancer Registry does not record information on receipt and completion of systemic therapies,(16) genetic conditions,(30) microsatellite instability, (31) family history,(47) lifestyle,(32, 48) environmental exposures(49) and surveillance intensity.(50) In particular we lacked information to determine what effect, if any, radiation treatment for the first cancer had on the risk of subsequent cancers.

Conjecture regarding the association between CRC and other types of cancer needs to be considered within the limitations of our study. Common risk factors (9, 14, 30, 43) and incidental diagnosis of subsequent cancers during increased medical surveillance of CRC patients may explain at least some of the observed site-specific associations. However our study design and available data precluded further investigation into these topics. It is also possible that the significantly increased risk for colon and lung cancers over all age groups may be indicative of the higher number of cases compared to some other sites. Risk comparisons across cohorts can also be misleading due to variations in treatment, disparities in the distribution of underlying risk factors and differences in the definition used for multiple primary cancers.

Finally, distinguishing statistical artifacts from biologically plausible associations can be complicated by systematic biases inherent in follow up studies of cancer patients.(19, 50) Surveillance bias has been reduced by considering only MPCs diagnosed more than two months after the initial CRC.(19) The study population was

restricted to first primary CRC cases thereby avoiding potential treatment-related effects for a previous cancer. The high level of histological confirmation for cancers recorded by the Queensland Cancer Registry (90% in 2008)(17) also reflects a low likelihood that metastases from the original cancer would be classified as a new primary.

*Conclusions*

Multiple primary tumours are expected to become a more prevalent threat in the future with longer life expectancy and improved survival after a cancer diagnosis.(3) This study found increased risks among younger patients, within the first year of diagnosis, for colon cancer survivors and those who have had surgical treatment. Efforts to quantify and characterize these risks have important implications for reducing incidence and burden of MPCs through early identification and preventive strategies among cancer survivors. While these population-based results do not incorporate all possible risk factors, by quantifying the independent associations that key demographic and clinical factors have on the risk of multiple primary cancers for CRC patients, they form an important foundation from which to expand our knowledge in this area.

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Table 1: Relative risk of MPCs more than 2 months after CRC diagnosis by sex in Queensland, 1996-2007.

| | Persons | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Obs[a] | SIR[b] (95%CI)[c] | Obs. | SIR (95%CI) | Obs. | SIR (95%CI) |
| Stomach (C16) | 38 | **1.43 (1.01, 1.97)** [d] | 29 | 1.44 (0.97, 2.07) | 9 | 1.39 (0.64, 2.64) |
| Small Intestine (C17) | 20 | **4.84 (2.96, 7.48)** | 15 | **5.75 (3.22, 9.48)** | 5 | **3.29 (1.07, 7.67)** |
| Colorectal (C18-C20, C218) | 273 | **1.47 (1.30, 1.66)** | 147 | **1.23 (1.04, 1.45)** | 126 | **1.91 (1.59, 2.28)** |
| Colon (C18) | 218 | **1.73 (1.51, 1.98)** | 120 | **1.56 (1.29, 1.86)** | 98 | **2.01 (1.63, 2.45)** |
| Rectum (C19-C20, C218) | 55 | 0.89 (0.67, 1.16) | 27 | *0.62 (0.41, 0.90)*[e] | 28 | **1.55 (1.03, 2.24)** |
| Pancreas (C25) | 33 | 1.19 (0.82, 1.67) | 19 | 1.09 (0.66, 1.71) | 14 | 1.34 (0.73, 2.24) |
| Lung (C33, C34) | 202 | **1.40 (1.22, 1.61)** | 147 | **1.35 (1.14, 1.58)** | 55 | **1.57 (1.19, 2.05)** |
| Melanoma (C44, M872-M879) | 168 | **1.37 (1.17, 1.59)** | 124 | **1.42 (1.18, 1.69)** | 44 | 1.25 (0.91, 1.67) |
| Breast-female (C50) | 115 | **1.22 (1.01, 1.47)** | n.a[f] | n.a. | 113 | **1.22 (1.01, 1.47)** |
| Uterus (C54) | 25 | **1.57 (1.01, 2.31)** | n.a. | n.a. | 25 | **1.57 (1.01, 2.31)** |
| Prostate (C60-C63) | 265 | **1.14 (1.01, 1.29)** | 265 | **1.14 (1.01, 1.29)** | n.a. | n.a. |
| Kidney (C64-C66, C68) | 57 | **1.61 (1.21, 2.07)** | 36 | **1.46 (1.02, 2.02)** | 21 | **1.90 (1.18, 2.91)** |
| Bladder (C67) | 73 | 1.25 (0.98, 1.57) | 63 | **1.31 (1.01, 1.68)** | 10 | 0.98 (0.47, 1.80) |
| Unknown (C26, C39, C76, C77, C80) | 27 | *0.65 (0.43, 0.94)*[g] | 20 | 0.74 (0.45, 1.14) | 7 | *0.47 (0.19, 0.98)* |
| Non-Hodgkin lymphoma (M967-M972) | 42 | 1.02 (0.73, 1.38) | 28 | 1.08 (0.72, 1.57) | 14 | 0.91 (0.50, 1.52) |
| Lymphoid leukaemia (M982-M983) | 21 | 1.30 (0.80, 1.99) | 16 | 1.46 (0.83, 2.37) | 5 | 0.96 (0.31, 2.25) |
| Myeloma (M973) | 21 | 1.32 (0.82, 2.02) | 15 | 1.43 (0.80, 2.36) | 6 | 1.11 (0.41, 2.41) |
| Myelodysplastic disease (M998) | 24 | **1.66 (1.06, 2.47)** | 17 | 1.69 (0.99, 2.71) | 7 | 1.58 (0.63, 3.25) |
| All cancers (C00-C80) | 1,615 | **1.28 (1.22, 1.34)** | 1,086 | **1.25 (1.18, 1.33)** | 529 | **1.34 (1.22, 1.45)** |
| All cancers but colorectal cancers (C00-C17, C22-C80) | 1,342 | **1.24 (1.18, 1.31)** | 939 | **1.25 (1.18, 1.34)** | 403 | **1.22 (1.10, 1.35)** |

[a] Obs.=Observed number of multiple primary cancers; [b] SIR=standardized incidence ratio; [c] CI=confidence interval; [d] SIRs shown in normal bold font indicate significant increased risk; [e]SIRs shown in normal italics indicate significant decreased risk (significant means 95%CI does not include 1; [f] n.a.=not applicable.

Table 2: Relative risk of MPCs more than 2 months after CRC diagnosis by age at first diagnosis in Queensland, 1996-2007.

| | Age group at first diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | 20-59 | | 60-69 | | 70-79 | |
| | Obs[a.] | SIR[b] (95%CI)[c] | Obs. | SIR (95%CI) | Obs. | SIR (95%CI) |
| Stomach (C16) | [f] | [f] | 16 | **1.82 (1.04, 2.95)[d]** | 19 | 1.29 (0.78, 2.01) |
| Small Intestine (C17) | [f] | [f] | 8 | **5.35 (2.31, 10.55)** | 9 | **4.65 (2.12, 8.82)** |
| Colorectal (C18-C20, C218) | 46 | **1.85 (1.35, 2.47)** | 101 | **1.49 (1.21, 1.81)** | 126 | **1.36 (1.13, 1.62)** |
| Colon (C18) | 35 | **2.35 (1.64, 3.27)** | 75 | **1.67 (1.31, 2.09)** | 108 | **1.63 (1.34, 1.97)** |
| Rectum (C19-C20, C218) | 11 | 1.06 (0.53, 1.90) | 26 | 1.09 (0.71, 1.60) | 18 | 0.65 (0.39, 1.03) |
| Pancreas (C25) | [f] | [f] | 14 | 1.51 (0.83, 2.54) | 15 | 0.98 (0.55, 1.62) |
| Lung (C33, C34) | 31 | **1.73 (1.17, 2.45)** | 74 | **1.37 (1.08, 1.72)** | 97 | **1.34 (1.09, 1.64)** |
| Melanoma (C44, M872-M879) | 30 | 1.14 (0.77, 1.62) | 61 | **1.41 (1.08, 1.81)** | 77 | **1.45 (1.14, 1.81)** |
| Breast-female (C50) | 28 | 1.07 (0.71, 1.54) | 41 | 1.24 (0.89, 1.69) | 46 | 1.32 (0.96, 1.76) |
| Uterus (C54) | 11 | **3.03 (1.51, 5.42)** | 6 | 1.04 (0.38, 2.26) | 8 | 1.22 (0.53, 2.41) |
| Prostate (C60-C63) | 39 | 1.24 (0.88, 1.69) | 113 | **1.21 (1.01, 1.46)** | 113 | 1.05 (0.86, 1.26) |
| Kidney (C64-C66, C68) | 9 | 1.60 (0.73, 3.04) | 22 | **1.73 (1.08, 2.61)** | 26 | 1.50 (0.98, 2.20) |
| Bladder (C67) | 11 | 1.85 (0.93, 3.32) | 22 | 1.09 (0.69, 1.66) | 40 | 1.24 (0.89, 1.69) |
| Unknown (C26, C39, C76, C77, C80) | 5 | 1.12 (0.36, 2.62) | 12 | 0.91 (0.47, 1.59) | 10 | *0.41 (0.20, 0.76)*[e] |
| Non-Hodgkin lymphoma (M967-M972) | 6 | 0.90 (0.33, 1.97) | 11 | 0.78 (0.39, 1.39) | 25 | 1.22 (0.79, 1.80) |
| Lymphoid leukaemia (M982-M983) | [f] | [f] | 8 | 1.36 (0.59, 2.68) | 10 | 1.29 (0.62, 2.38) |
| Myeloma (M973) | 5 | 2.44 (0.79, 5.69) | 6 | 1.11 (0.41, 2.42) | 10 | 1.18 (0.57, 2.18) |
| Myelodysplastic disease (M998) | [f] | [f] | 8 | 2.03 (0.88, 4.00) | 13 | 1.35 (0.72, 2.31) |
| All cancers (C00-C80) | 277 | **1.38 (1.22, 1.55)** | 591 | **1.29 (1.19, 1.40)** | 747 | **1.23 (1.15, 1.32)** |
| All cancers but colorectal cancers (C00-C17, C22-C80) | 231 | **1.32 (1.15, 1.50)** | 490 | **1.26 (1.15, 1.37)** | 621 | **1.21 (1.12, 1.31)** |

[a] Obs.=Observed number of multiple primary cancers; [b] SIR=standardized incidence ratio; [c] CI=confidence interval; [d] SIRs shown in normal bold font indicate significant increased risk;[e] SIRs shown in normal italics indicate significant decreased risk (significant means 95%CI does not include 1);[f] Estimates not shown for cancers of the stomach, pancreas and small intestine ; myelodysplastic disease and lymphoid leukemia for age group 20 to 59 years due to an observed count of less than 5.

Table 3: Relative risk of MPCs more than 2 months after CRC diagnosis in by follow-up period Queensland, 1996-2007.

| | Year(s) after first diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | <1 | | **1-5** | | **> 5** | |
| | Obs[a.] | SIR[b] (95%CI)[c] | Obs. | SIR (95%CI) | Obs. | SIR (95%CI) |
| Stomach (C16) | 7 | 1.56 (0.63, 3.22) | 17 | 1.25 (0.73, 2.00) | 14 | **1.84 (1.01, 3.09)[d]** |
| Small Intestine (C17) | 7 | 5.02 (2.65, 8.25) | 10 | **4.58 (2.20, 8.43)** | [j] | [j] |
| Colorectal (C18-C20, C218) | 98 | **2.91 (2.37, 3.55)** | 122 | **1.26 (1.04, 1.50)** | 53 | 1.04 (0.78, 1.36) |
| Colon (C18) | 75 | **3.35 (2.64, 4.20)** | 97 | **1.48 (1.20, 1.81)** | 46 | 1.31 (0.96, 1.75) |
| Rectum (C19-C20, C218) | 23 | **1.97 (1.25, 2.96)** | 25 | 0.76 (0.49, 1.13) | 7 | *0.43 (0.17, 0.88)[e]* |
| Pancreas (C25) | [f] | [f] | 23 | **1.61 (1.02, 2.42)** | 6 | 0.75 (0.28, 1.64) |
| Lung (C33, C34) | 41 | **1.56 (1.12, 2.11)** | 99 | **1.31 (1.06, 1.59)** | 62 | **1.59 (1.22, 2.04)** |
| Melanoma (C44, M872-M879) | 33 | 1.41 (0.97, 1.97) | 75 | 1.15 (0.90, 1.44) | 60 | **1.85 (1.42, 2.39)** |
| Breast-female (C50) | 14 | 0.77 (0.42, 1.29) | 69 | **1.37 (1.07, 1.73)** | 32 | 1.28 (0.87, 1.80) |
| Uterus (C54) | 5 | 1.65 (0.54, 3.85) | 11 | 1.29 (0.65, 2.31) | 9 | 2.09 (0.95, 3.96) |
| Prostate (C60-C63) | 48 | 1.11 (0.82, 1.47) | 136 | 1.11 (0.93, 1.31) | 81 | **1.32 (1.04, 1.64)** |
| Kidney (C64-C66, C68) | 18 | 2.73 (1.62, 4.31) | 24 | 1.28 (0.82, 1.90) | 15 | 1.56 (0.87, 2.57) |
| Bladder (C67) | 16 | 1.59 (0.91, 2.58) | 38 | 1.26 (0.89, 1.73) | 19 | 1.16 (0.70, 1.81) |
| Unknown (C26, C39, C76, C77, C80) | [f] | [f] | 15 | 0.71 (0.40, 1.17) | 9 | 0.73 (0.33, 1.39) |
| Non-Hodgkin lymphoma (M967-M972) | 7 | 0.94 (0.38, 1.95) | 26 | 1.21 (0.79, 1.77) | 9 | 0.79 (0.36, 1.50) |
| Lymphoid leukaemia (M982-M983) | 5 | 1.69 (0.55, 3.95) | 12 | 1.42 (0.73, 2.48) | [g] | [g] |
| Myeloma (M973) | [f] | [f] | 12 | 1.47 (0.76, 2.56) | 8 | 1.78 (0.77, 3.50) |
| Myelodysplastic disease (M998) | [f] | [f] | 11 | 1.55 (0.77, 2.77) | 9 | 2.01 (0.91, 3.79) |
| All cancers (C00-C80) | 347 | **1.51 (1.35, 1.67)** | 813 | **1.23 (1.14, 1.31)** | 455 | **1.32 (1.21, 1.45)** |
| All cancers but colorectal cancers (C00-C17, C22-C80) | 249 | **1.26 (1.11, 1.43)** | 691 | **1.22 (1.13, 1.31)** | 402 | **1.37 (1.24, 1.51)** |

[a] Obs.=Observed number of multiple primary cancers; [b] SIR=standardized incidence ratio; [c] CI=confidence interval; [d] SIRs shown in normal bold font indicate significant increased risk; [e]SIRs shown in normal italics indicate significant decreased risk (significant means 95%CI does not include 1); [f] Estimates not shown for cancers of pancreas and unknown primary site; myelodysplastic disease and myeloma for less than 1 year follow-up due to an observed count of less than 5; [g] Estimates not shown for cancers of small intestine and lymphoid leukemia for more than 5 years follow-up due to an observed count of less than 5.

Table 4 Relative risk ratios from multivariable Poisson regression [a] for MPCs after CRC in Queensland, 1996-2007.

| | N (%) | All cancers (1,615)[b] RRR[c] (95%CI)[d] | All sites but colorectal cancer (1,342) RRR (95%CI) |
|---|---|---|---|
| **Sex** | | | |
| Male | 9,089 (57.7) | 1.00 | 1.00 |
| Female | 6,666 (42.3) | 1.02 (0.92, 1.13) | 0.93 (0.83, 1.05) |
| p value | | 0.735 | 0.219 |
| **Age group at first diagnosis** | | | |
| 20-59 | 4,907 (31.1) | 1.23 (1.07, 1.41) | 1.17 (1.02, 1.37) |
| 60-69 | 5,193 (33.0) | 1.09 (0.98, 1.22) | 1.07 (1.01, 1.20) |
| 70-79 | 5,655 (35.9) | 1.00 | 1.00 |
| p value | | **0.005**[e] | **0.018** |
| **Year(s) after first diagnosis** | | | |
| <1 | 2,637 (16.7) | 1.00 | 1.00 |
| 1-5 | 7,114 (45.2) | 0.82 (0.72, 0.92) | 0.97 (0.84, 1.12) |
| >5 | 6,004 (38.1) | 0.88 (0.77, 0.98) | 1.09 (0.93, 1.28) |
| p value | | **0.006** | 0.163 |
| **Initial cancer site**[f] | | | |
| Proximal Colon | 5,171 (32.8) | 1.45 (1.29, 1.64) | 1.41 (1.24, 1.62) |
| Distal Colon | 4,007 (25.4) | 1.24 (1.09, 1.41) | 1.16 (1.01, 1.35) |
| Unknown Colon | 847 (5.4) | 1.32 (1.02, 1.66) | 1.38 (1.05, 1.77) |
| Rectal | 5,730 (36.4) | 1.00 | 1.00 |
| p value | | **<0.001** | **<0.001** |
| **Initial cancer stage** | | | |
| Early (Stage 1-II) | 7,685 (48.8) | 1.07 (0.95, 1.20) | 1.10 (0.97, 1.25) |
| Advanced (Stage III-IV) | 5,681 (36.1) | 1.00 | 1.00 |
| Unknown | 2,389 (15.1) | 1.03 (0.87, 1.22) | 1.12 (0.93, 1.34) |
| p value | | 0.480 | 0.301 |
| **Surgical Treatment** | | | |
| No/Unknown | 2,137 (13.5) | 1.00 | 1.00 |
| Yes | 13,618 (86.5) | 1.33 (1.13, 1.57) | 1.26 (1.05, 1.50) |
| p value | | **<0.001** | **0.011** |
| **Diabetes** | | | |
| No | 12,493 (79.3) | 1.00 | 1.00 |
| Yes | 1,125 (7.2) | 1.17 (0.98, 1.41) | 1.19 (0.98, 1.44) |
| Unknown[g] | 2,137 (13.5) | - | - |
| p value | | 0.078 | 0.077 |

[a] Estimates adjusted for sex, age group at first diagnosis, follow-up time; initial cancer site, stage, surgical treatment and diabetes; [b]Observed number of multiple primary cancers in brackets; [c] RRR=relative rate ratio; [d] CI=confidence interval; [e.] p values in bold are significant; [f] Colorectal sites defined as: proximal colon (C180 to C184), distal colon (C185-C187), unspecified colon (C188-C189) and rectal (C19-C20, C218); [g] Omitted due to co-linearity with no/unknown surgical treatment category.

Table 5 Relative risk ratios from multivariable Poisson regression [a] for MPCs after CRC by selected cancer sites in Queensland, 1996-2007.

| | Colorectal (273) RRR[b] (95%CI)[c] | Lung (202) RRR (95%CI) | Melanoma (168) RRR (95%CI) | Kidney (57) RRR (95%CI) | Bladder (73) RRR (95%CI) | Breast (115) RRR (95%CI) | Prostate (285) RRR (95%CI) |
|---|---|---|---|---|---|---|---|
| **Sex** | | | | | | | |
| Male | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | | |
| Female | 1.53 (1.20, 1.96) | 1.12 (0.80, 1.57) | 0.84 (0.59, 1.20) | 1.27 (0.73, 2.19) | 0.71 (0.36, 1.38) | | |
| p value | **<0.001**[d] | 0.495 | 0.336 | 0.396 | 0.311 | | |
| **Age group at first diagnosis** | | | | | | | |
| 20-59 | 1.74 (1.23, 2.45) | 1.41 (0.92, 2.15) | 0.83 (0.54, 1.27) | 1.30 (0.60, 2.80) | 1.80 (0.91, 3.55) | 0.80 (0.50, 1.30) | 1.27 (0.87, 1.83) |
| 60-69 | 1.26 (0.97, 1.64) | 1.05 (0.76, 1.46) | 0.98 (0.70, 1.39) | 1.28 (0.72, 2.28) | 0.95 (0.56, 1.61) | 0.89 (0.58, 1.36) | 1.2 (0.92, 1.56) |
| 70-79 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| p value | **0.006** | 0.288 | 0.671 | 0.647 | 0.189 | 0.661 | 0.272 |
| **Year(s) after first diagnosis** | | | | | | | |
| <1 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1-5 | 0.42 (0.32, 0.55) | 0.83 (0.57, 1.23) | 0.82 (0.54, 0.93) | 0.45 (0.24, 0.83) | 0.81 (0.45, 1.45) | 2.11 (1.14, 3.90) | 1.01 (0.72, 1.41) |
| >5 | 0.34 (0.25, 0.48) | 1.00 (0.66, 1.53) | 1.34 (0.87, 2.08) | 0.52 (0.26, 1.05) | 0.75 (0.38, 1.47) | 1.98 (1.02, 3.86) | 1.18 (0.82, 1.70) |
| p value | **<0.001** | 0.465 | **0.021** | **0.031** | 0.684 | **0.033** | 0.495 |
| **Initial cancer site**[e] | | | | | | | |
| Proximal Colon | 1.69 (1.24, 2.30) | 0.97 (0.68, 1.39) | 1.41 (0.96, 2.07) | 1.60 (0.84, 3.08) | 2.10 (1.16, 3.81) | 1.16 (0.72, 1.87) | 1.66 (1.22, 2.24) |
| Distal Colon | 1.70 (1.23, 2.35) | 0.88 (0.60, 1.30) | 1.14 (0.74, 1.73) | 1.38 (0.70, 2.77) | 1.67 (0.89, 3.14) | 1.27 (0.77, 2.11) | 1.44 (1.05, 1.97) |
| Unknown Colon | 0.84 (0.38, 1.83) | 1.23 (0.66, 2.31) | 1.68 (0.86, 3.26) | 0.87 (0.20, 3.85) | 1.64 (0.55, 4.92) | 1.57 (0.71, 3.48) | 1.35 (0.98, 2.82) |
| Rectal | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| p value | **0.001** | 0.779 | 0.224 | 0.499 | 0.109 | 0.656 | **0.008** |
| **Initial cancer stage** | | | | | | | |
| Early | 0.96 (0.74, 1.25) | 1.23 (0.86, 1.75) | 1.18 (0.81, 1.70) | 1.83 (0.92, 3.69) | 0.92 (0.54, 1.57) | 0.92 (0.60, 1.42) | 1.10 (0.82, 1.48) |
| Advanced | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Unknown | 0.63 (0.39, 1.01) | 0.97 (0.58, 1.62) | 0.81 (0.46, 1.44) | 1.33 (0.53, 3.81) | 1.11 (0.52, 2.36) | 1.01 (0.54, 1.86) | 1.28 (0.86, 1.91) |
| p value | 0.146 | 0.370 | 0.304 | 0.217 | 0.851 | 0.920 | 0.470 |
| **Surgical Treatment** | | | | | | | |
| No/Unknown | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.91 (1.18, 3.09) | 1.55 (0.93, 2.59) | 1.19 (0.73, 1.94) | 0.76 (0.37, 1.57) | 1.11 (0.52, 2.36) | 0.99 (0.57, 1.69) | 1.28 (0.86, 1.90) |
| p value | **0.009** | 0.095 | 0.494 | 0.456 | 0.789 | 0.9551 | 0.224 |
| **Diabetes** | | | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.08 (0.70, 1.66) | 1.41 (0.89, 2.23) | 1.07 (0.61, 1.89) | 1.28 (0.50, 3.26) | 2.02 (1.04, 3.88) | 0.98 (0.43, 2.26) | 1.07 (0.68, 1.64) |
| Unknown[f] | | | | | | | |
| p value | 0.732 | 0.145 | 0.841 | 0.605 | **0.037** | 0.968 | 0.809 |

[a] Estimates adjusted for sex, age group at first diagnosis, follow-up time; initial cancer site, stage, surgical treatment and diabetes; [b] RRR=relative rate ratio; [c] CI=confidence interval; [d.] p values in bold are significant; [e] Colorectal sites defined as: proximal colon (C180 to C184), distal colon (C185-C187), unspecified colon (C188-C189) and rectal (C19-C20, C218); [f] Omitted due to co-linearity with no/unknown surgical treatment category.