



Review of colorectal cancer in the ACT

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1. Executive summary

Colorectal cancer was the second most common cancer in both males and females in the ACT accounting for 13% of cancers in 2004-08.

Incidence

- Over the five-year period 2004-08, the annual crude incidence was 58 cases per 100,000 for males and 48 for females. This represented an average of 96 new cases per year for males and 82 for females.
- In 2004-08, the risk of developing colorectal cancer before the age of 85 years was 1 in 11 for males and 1 in 14 for females.
- The median age of diagnosis was 66 years for males and 70 years for females.
- Males had a higher incidence rate than females in the entire period 1985-2008. There was no significant change in the incidence trend detected in either males or females.
- Incidence rate of colorectal cancer in the ACT (59.1 per 100,000 population) was the third lowest as compared to other jurisdictions, and slightly lower than the national estimate (62.3).

Prevalence

- Colorectal cancer is the second most prevalent type of cancer in the ACT.
- As at the end of 2007, there were 333 males and 294 females who were living in the ACT following a diagnosis of cancer within the previous five years.

Risk factors

- A number of the risk factors for developing colorectal cancer are life-style related and are modifiable. These include lack of exercise, obesity, excessive alcohol consumption, tobacco smoking and unhealthy diet.
- A large proportion of ACT residents was either overweight or obese; had insufficient physical activity and consumed excessive amount of alcohol.
- A greater proportion of males than females in the ACT engaged in health risk behaviours that may promote the development of colorectal cancer. These included excessive alcohol consumption, insufficient intake of fruits and vegetables, and being overweight or obese.

Mortality

- Colorectal cancer was the fourth most common cause of death among ACT residents during 2003-07.
- Over the five-year period, the crude mortality rate was 19.5 deaths per 100,000 males and 15.2 for females. This represented an average of 32 deaths for males and 26 deaths for females per year in the ACT.
- In 2004-08, the risk of dying from colorectal cancer before the age of 85 years was 1 in 30 for males and 1 in 45 for females.
- The median age at death was 69 years for males and 75 years for females.
- The age-standardised mortality rate decreased significantly in both males and females from 1985 to 2008.
- The mortality rate of colorectal cancer in the ACT (18.4 per 100,000 population) was among the lowest when compared to other jurisdictions, and slightly lower than the national estimate (19.1).

Survival

- 5-year survival from colorectal cancer for ACT residents was 66%.
- Females (71%) had a slightly higher 5-year survival than males (63%).
- Localised colorectal cancer had a higher survival ratio (96%) than colorectal cancer with regional spread (69%).
- The 5-year survival in 2000-04 (69%) was not significantly higher than 1995-99 (64%).

Screening

- The National Bowel Cancer Screening Program was started in late 2006.
- The participation rate of the ACT was significantly higher than the rest of Australia during 2006-2008.

2. INTRODUCTION

Colorectal cancer, commonly called bowel cancer, is the second most common cancer in both men and women in Australia, including the ACT. It is a major public health problem among the more affluent countries such as USA, Australia, New Zealand, Japan, and Hong Kong.

2.1. Types of colorectal cancer

Around 95 per cent of colorectal cancers are adenocarcinomas, with the remaining 5 per cent including mucinous carcinomas and adenosquamous carcinomas.

2.2. Risk factors

The main risk factors for this cancer include:

- Increasing age
- Family history of colorectal cancer
- Lack of exercise
- Obesity
- Diabetes mellitus
- Excessive alcohol consumption
- Tobacco smoking
- Unhealthy diet
- Inflammatory bowel disease
- Inherited diseases (eg. Familial adenomatous polyposis, hereditary non-polyposis coli)

As most of these risk factors reflect life styles, many can be reduced or modified with public education and early interventions.

2.3. Purpose of this report

In order to assist policy makers and health professionals to plan and deliver appropriate services, this report examines the following perspectives of colorectal cancer:

- Incidence
- Mortality
- Time trends
- Survival
- Prevalence
- Screening
- Risk factors

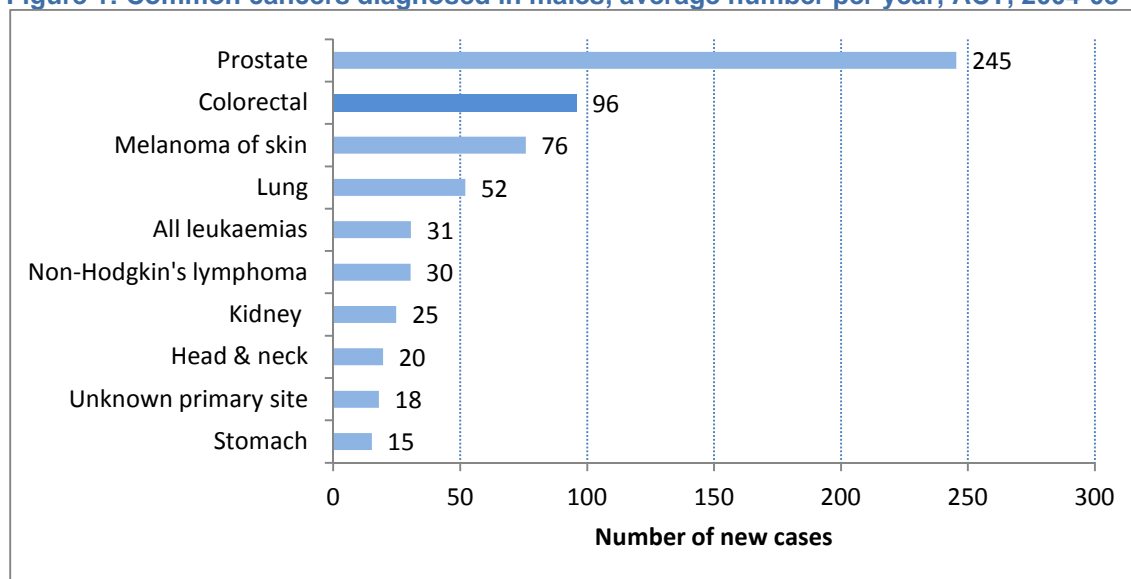
3. Incidence

3.1. Incidence at a glance

Colorectal cancer was the second most common cancer in both males and females in the ACT accounting for 13% of cancers in 2004-08. Over this period the annual crude incidence rate was 58 cases per 100,000 for males and 48 for females. This represented an average of 96 new cases per year for males and 82 for females (Figure 1 & 2). In 2004-08, the risk of developing colorectal cancer before the age of 85 years was 1 in 11 for males and 1 in 14 for females.

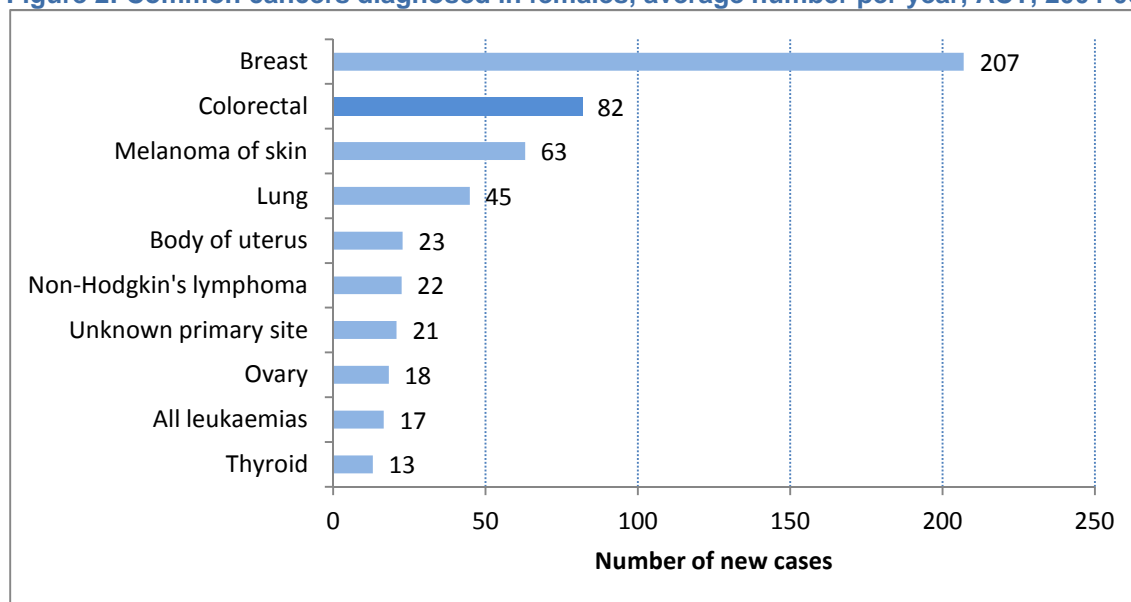
The ACT age-standardised rate for colorectal cancer was 71 cases per 100,000 for males and 53 for females. This rate was calculated using the Australian 2001 Standard Population and can be used for comparing the ACT with other jurisdictions.

Figure 1: Common cancers diagnosed in males, average number per year, ACT, 2004-08



Source: ACT Cancer Registry

Figure 2: Common cancers diagnosed in females, average number per year, ACT, 2004-08

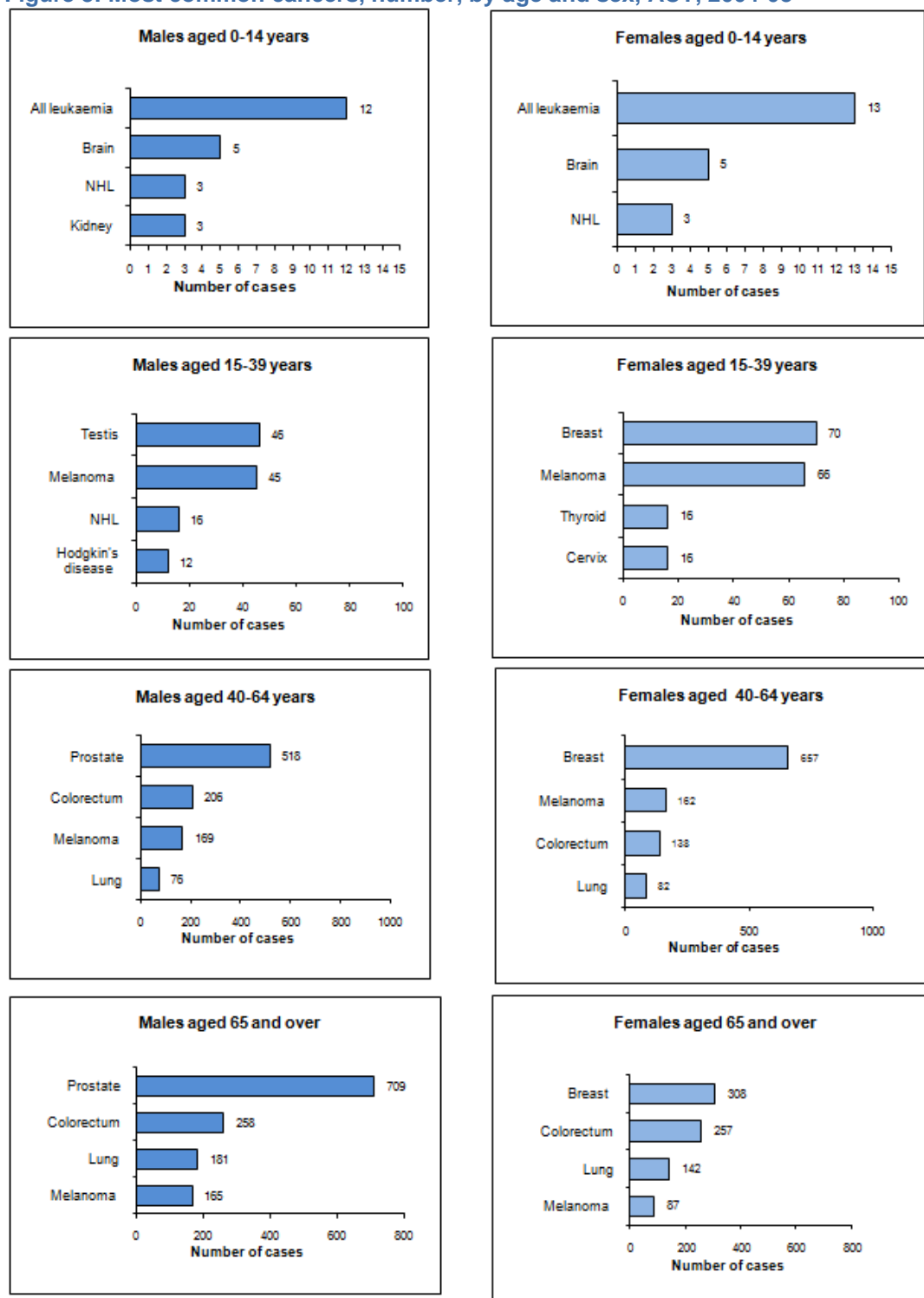


Source: ACT Cancer Registry

3.2. Most common cancers by age group

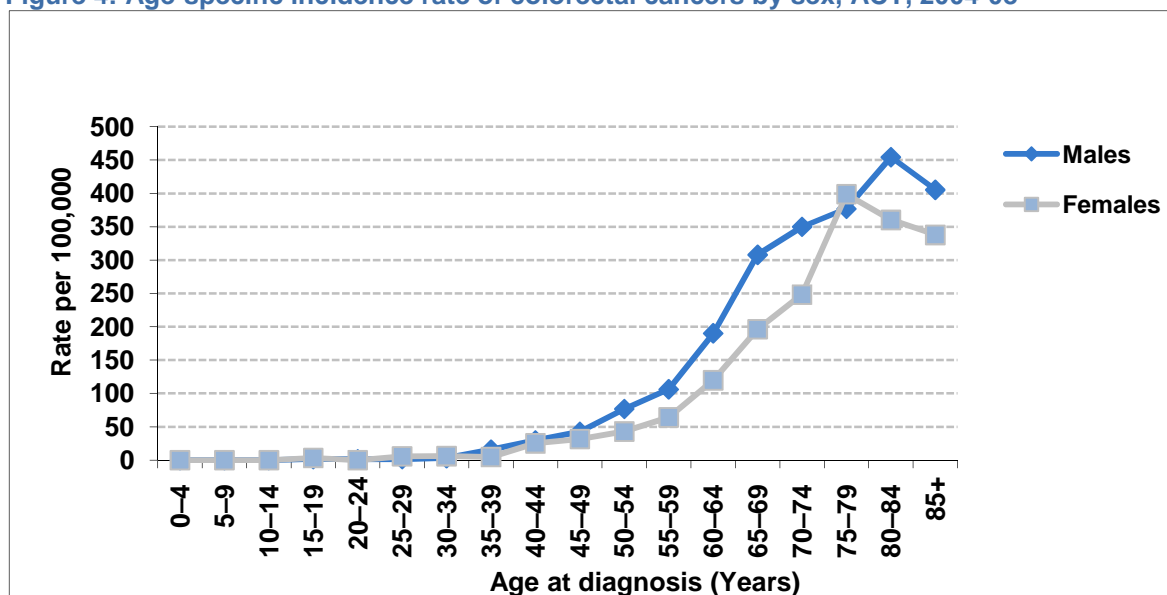
Colorectal cancer is uncommon among people younger than 35 years of age. Only 1.7 per cent of colorectal cancers were diagnosed in this age group in 2004-08. The proportion of colorectal cancer increased with age (Figure 3).

Figure 3: Most common cancers, number, by age and sex, ACT, 2004-08



Source: ACT Cancer Registry

Figure 4: Age-specific incidence rate of colorectal cancers by sex, ACT, 2004-08



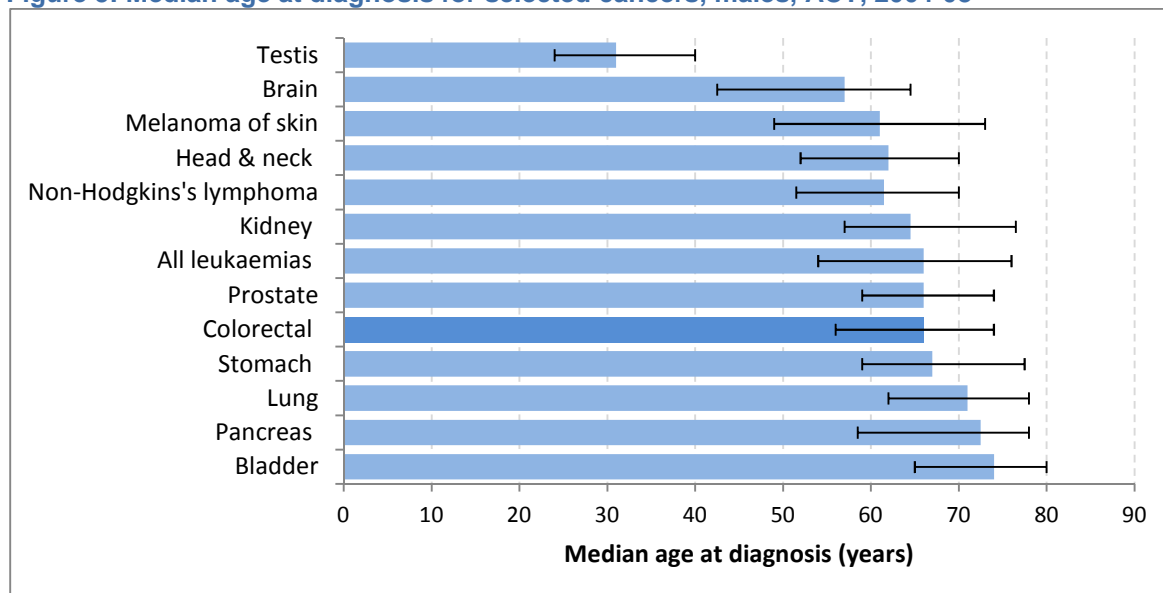
Note: Age-specific rate was an annualised average per 100,000 population for the period 2004-08.
 Source: ACT Cancer Registry

Diagnosis of colorectal cancer increased with age. Incidence rates were similar for males and females under the age of 50 years but increased more sharply for males between 50 and 75 years. A majority of the cases (71%) were diagnosed among people aged 60 years and over. Incidence rate peaked in 80-84 years for males and 75-79 years for females.

3.3. Median age at diagnosis

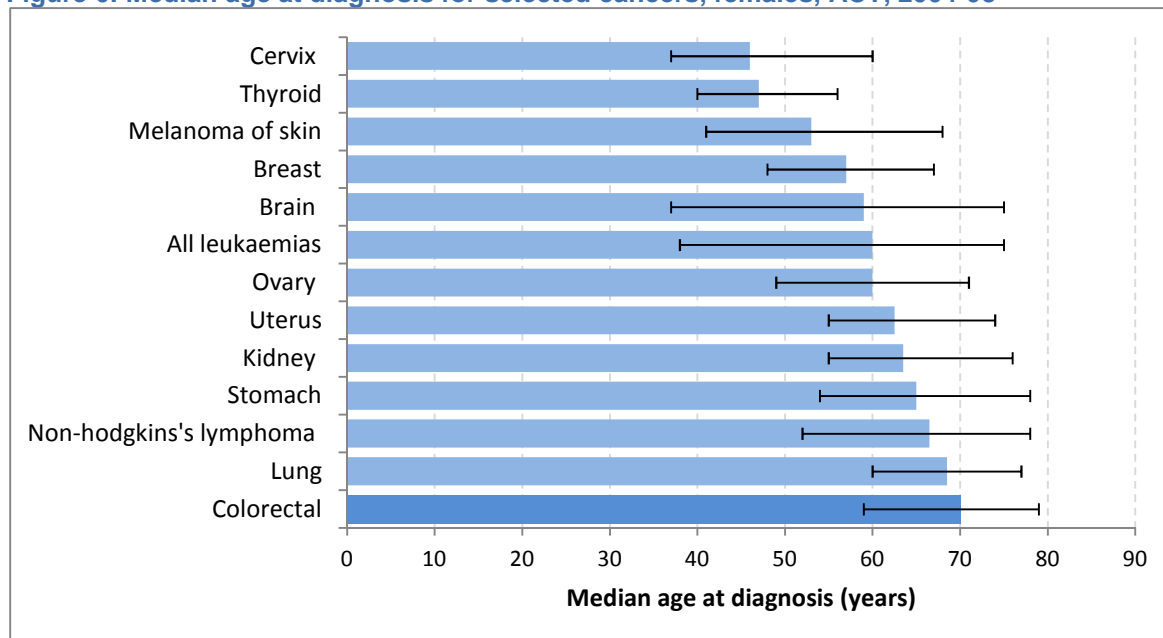
The median age of diagnosis of colorectal cancer was 66 years for males and 70 years for females (Figure 5 & 6).

Figure 5: Median age at diagnosis for selected cancers, males, ACT, 2004-08



Note: The median age, with the interquartile range (25% and 75%) indicated by the H bar.
Source: ACT Cancer Registry

Figure 6: Median age at diagnosis for selected cancers, females, ACT, 2004-08

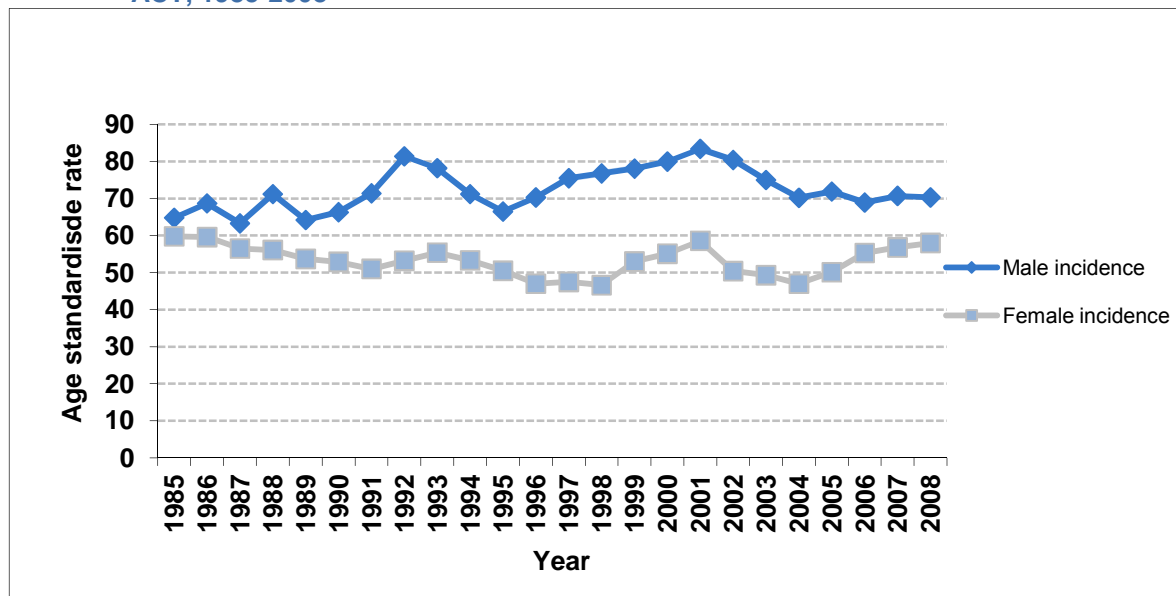


Note: The median age, with the interquartile range (25% and 75%) indicated by the H bar.
Source: ACT Cancer Registry

3.4. Incidence trends

The age-standardised incidence rates fluctuated in both genders over time without significant changes. Joinpoint analysis showed that there was an average decrease of incidence for males at 2% per year from 2001 to 2008. There was an average increase of incidence for females at 0.9% per year from 1995 to 2008. Overall, males had a higher incidence rate than females in the entire period (Figure 7).

Figure 7: Colorectal cancer, age-standardised incidence rates (3-year moving average), by sex, ACT, 1985-2008



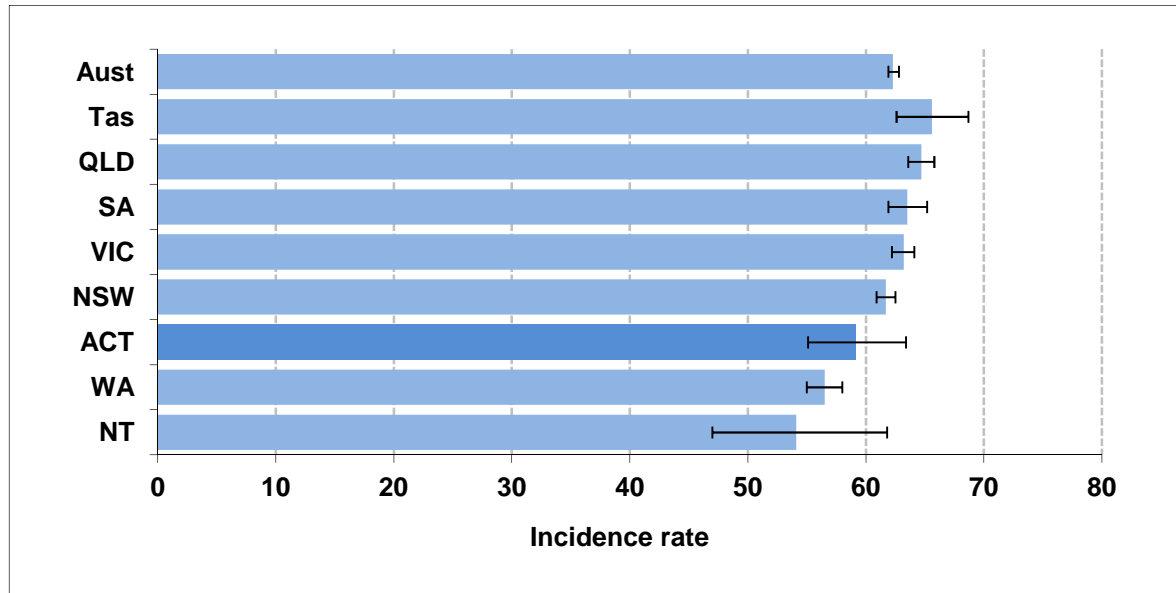
Note: Age-standardised rate per 100,000 population using the Australian Standard Population (2001) as the standard.

Source: ACT Cancer Registry

3.5. Interstate comparisons

The incidence rate of colorectal cancer in the ACT (59.1) was the third lowest compared to other states and territory, and slightly but not significantly lower than the national estimate (62.3) (Figure 8).

Figure 8: Colorectal cancer, average annual incidence rates (age-standardised) by states and territories, Australia, 2003-07



Notes: Age-standardised to the Australian population as at 30 June 2001.
Incidence rate expressed as number of cases per 100,000 population.

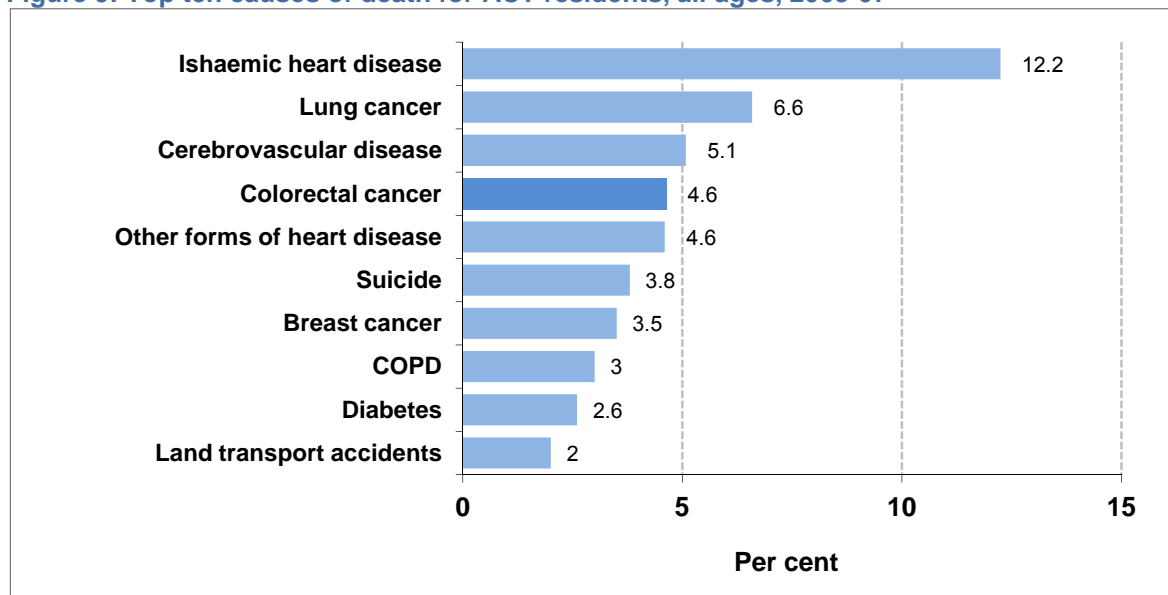
Source: Cancer in Australia an overview, 2010. AIHW cat. no. CAN56

4. Mortality

4.1. Mortality at a glance

Colorectal cancer was the fourth most common cause of death among ACT residents during 2003-07 (Figure 9).

Figure 9: Top ten causes of death for ACT residents, all ages, 2003-07

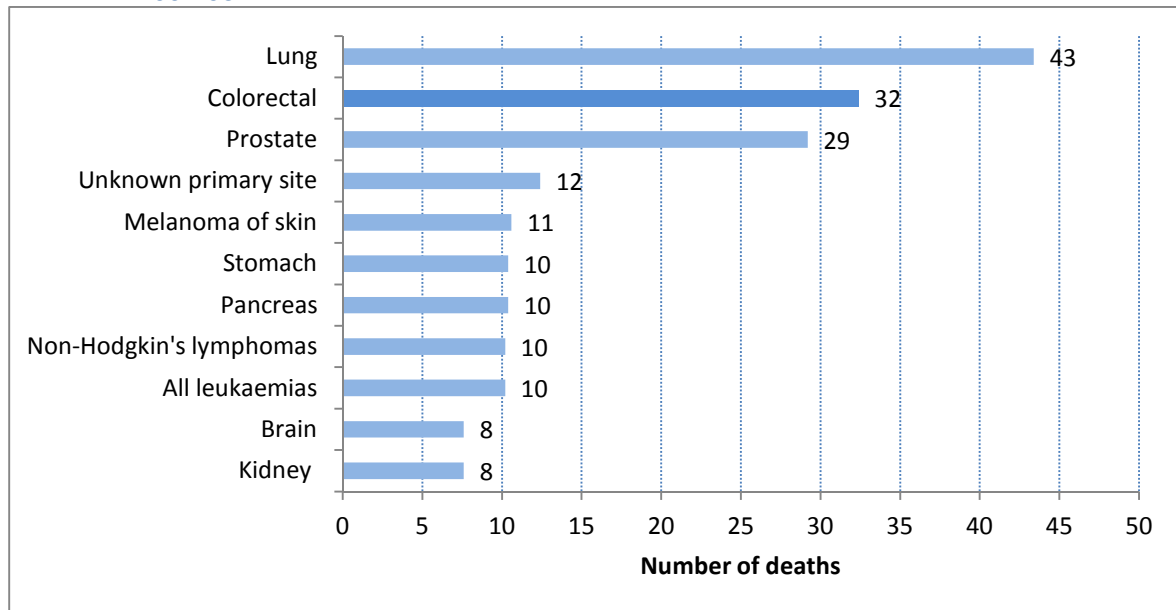


Source: Australian Bureau of Statistics, ACT causes of death, confidential unit record file, 2003-07.
Note: COPD= Chronic Obstructive Pulmonary Diseases

It was the second highest cause of cancer related deaths for males, and the third for females during 2004-08 (Figure 10 & 11). Over this period there was an average of 32 deaths related to colorectal cancer for males and 26 deaths for females each year in the ACT. The annual crude mortality rate was 19.5 deaths per 100,000 males and 15.2 for females. The risk of dying from colorectal cancer in the ACT was one in 30 for males and one in 45 for females before the age of 85 years.

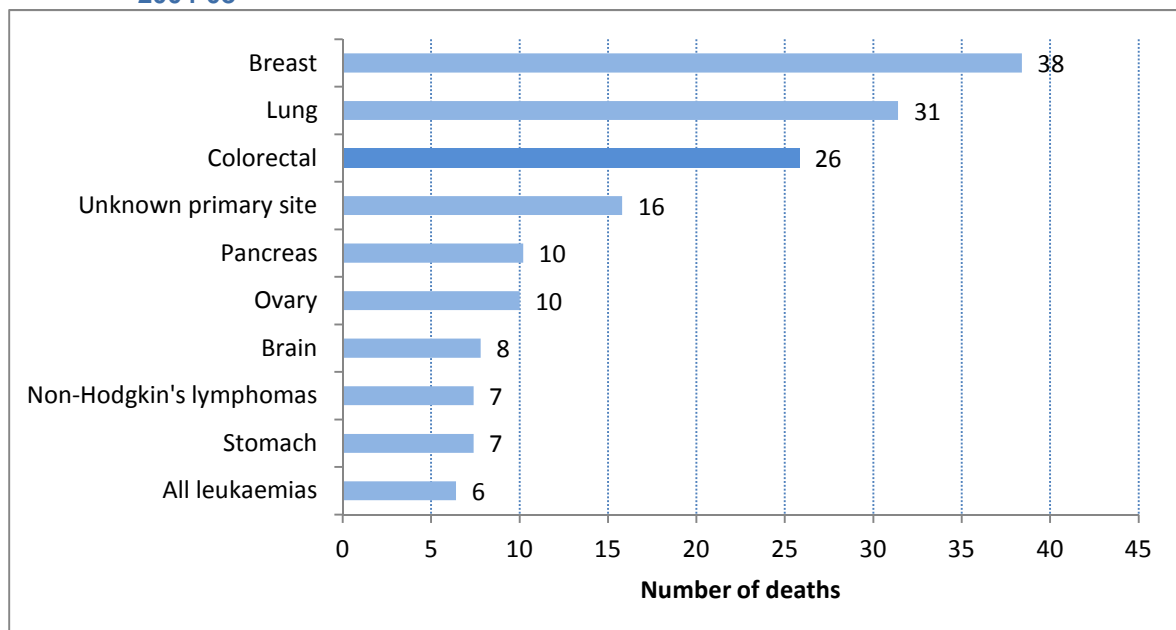
For comparative purposes the annual age-standardised mortality rate was 24 deaths per 100,000 males and 17 for females during 2004-08.

Figure 10: Common causes of cancer-related deaths, average number per year, males, ACT, 2004-08



Source: ACT Cancer Registry

Figure 11: Common causes of cancer-related deaths, average number per year, females, ACT, 2004-08

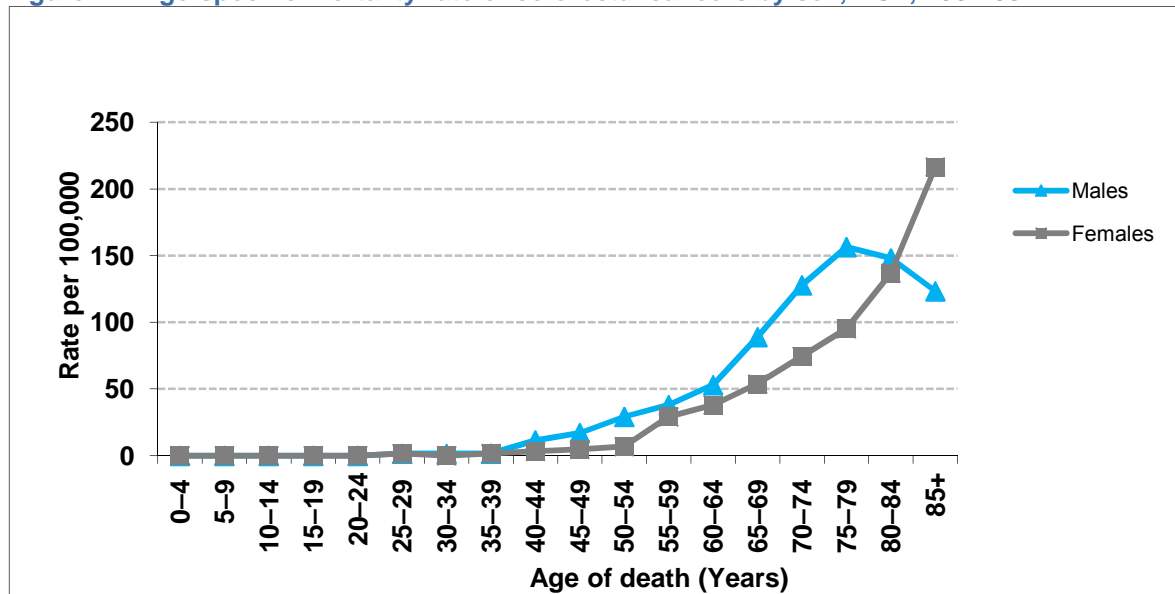


Source: ACT Cancer Registry

4.2. Most common cancer-related deaths by age group

Mortality due to colorectal cancer increased with age in both males and females. It reached its peak in 75-79 years in males and 85+ years in females (Figure 12).

Figure 12: Age-specific mortality rate of colorectal cancers by sex, ACT, 2004-08

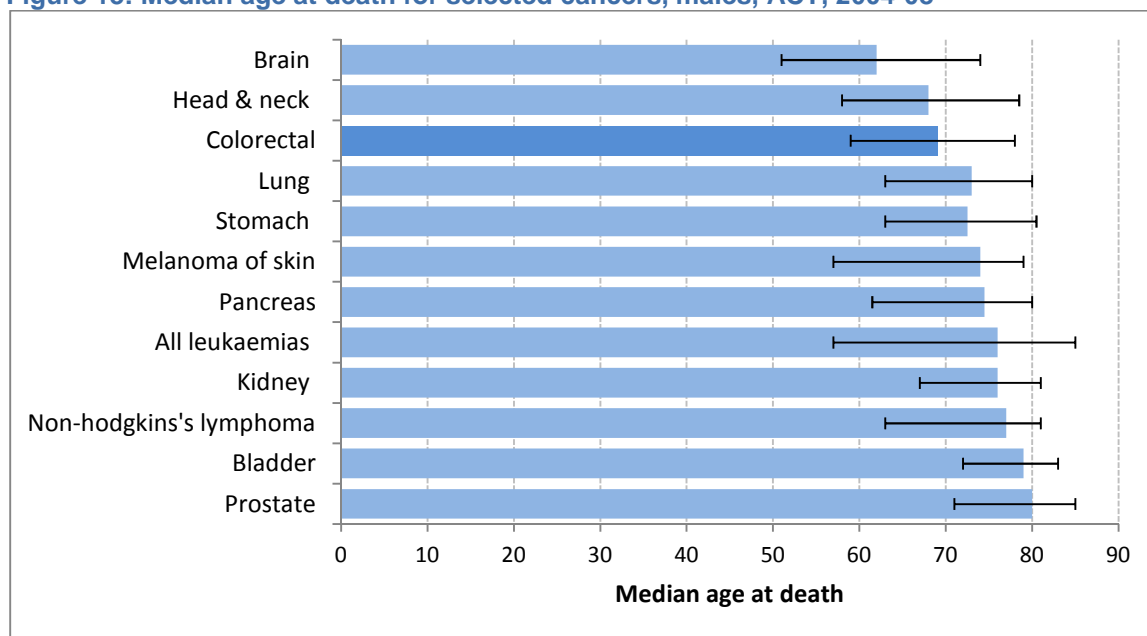


Note: Age-specific rate was an annualised average per 100,000 population for the period 2004-08.
Source: ACT Cancer Registry

4.3. Median age at death

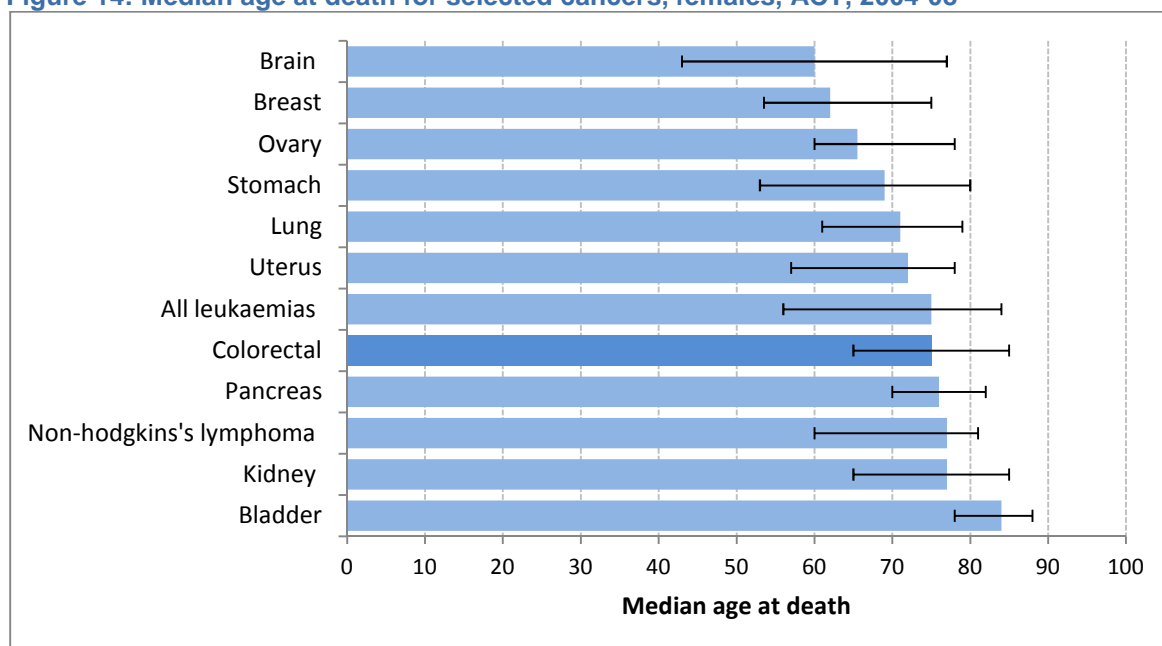
The median age at death for colorectal cancer was 69 years for males and 75 years for females (Figures 13 & 14).

Figure 13: Median age at death for selected cancers, males, ACT, 2004-08



Note: The median age, with the interquartile range (25% and 75%) indicated by the H bar.
Source: ACT Cancer Registry

Figure 14: Median age at death for selected cancers, females, ACT, 2004-08

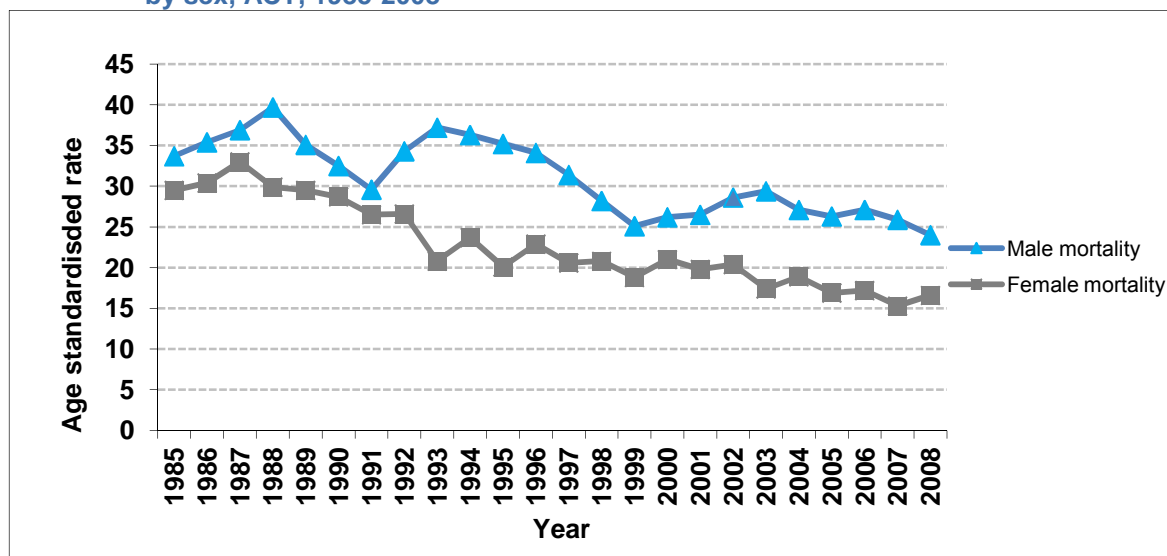


Note: The median age, with the interquartile range (25% and 75%) indicated by the H bar.
Source: ACT Cancer Registry

4.4. Mortality trends

The age-standardised mortality rate for colorectal cancer has decreased significantly in both males and females from 1985 to 2008. The male rate decreased at an average of 1.9 per cent per year ($p < 0.05$); female rate decreased at an average of 2.9 per cent per year ($p < 0.05$).

Figure 15: Colorectal cancer, age-standardised mortality rates (3-year moving average), by sex, ACT, 1985-2008



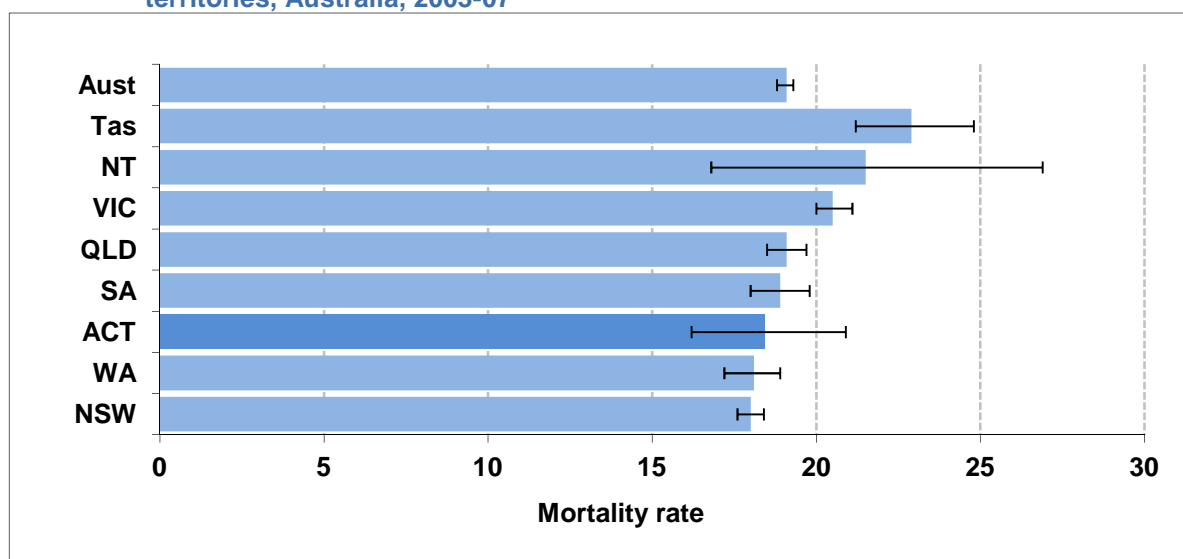
Note: Age-standardised rate per 100,000 population using the Australian Standard Population (2001) as the standard.

Source: ACT Cancer Registry

4.5. Interstate comparisons

The mortality rate of colorectal cancer in the ACT (18.4 per 100,000 population) was among the lowest compared to other jurisdictions, and slightly lower than the national estimate (19.1), but these differences were not significant.

Figure 16: Colorectal cancer, average annual mortality rates (age-standardised) by states and territories, Australia, 2003-07



Notes: Age-standardised to the Australian population as at 30 June 2001. Incidence rate expressed as number of cases per 100,000 population.

Source: Cancer in Australia an overview, 2010. AIHW cat. no. CAN56

5. Survival

Relative survival ratios were calculated using the period method to measure colorectal cancer survival in the ACT. This survival ratio describes the proportion of the observed survival rate to expected survival rate, expressed as a percentage.

The observed survival rate refers to colorectal cancer patients who would have survived to a certain time, usually five years for cancer, if the cancer they had was the only cause of death in the patient population. The expected survival rate refers to the expected rate of a group of people in the general population similar to the patient group with respect to ethnicity, age, sex and calendar period of observation.

5.1. Relative survival estimates

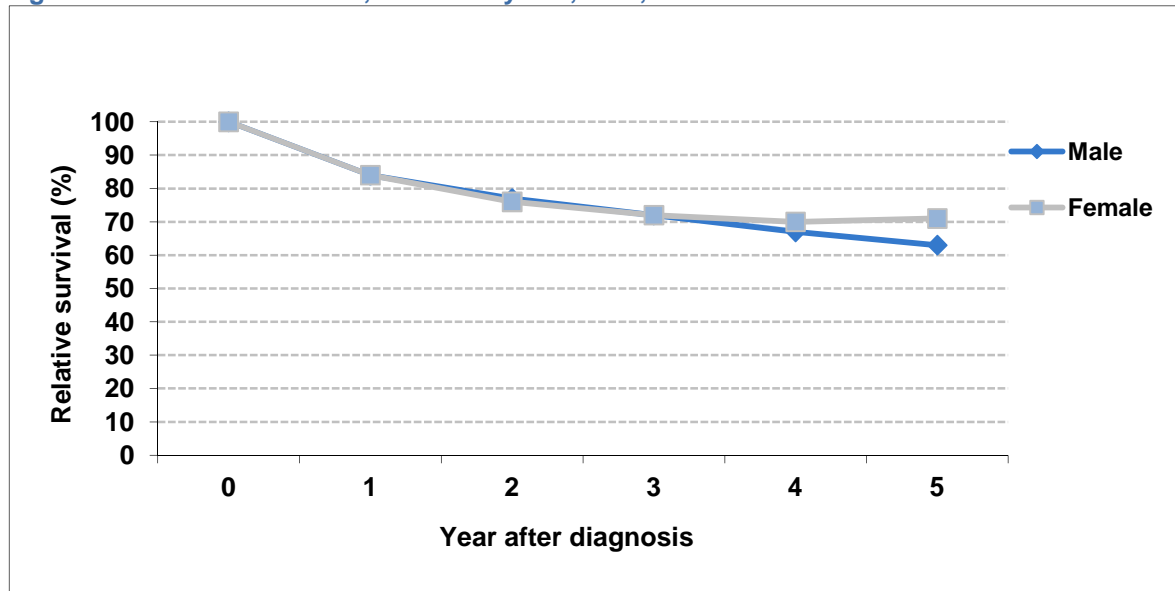
Table 1: Colorectal cancer, survival by years after diagnosis, by stage, sex, age group and selected period, ACT, 2000- 04

Year after diagnosis			Survival (%)	95% confidence interval
1			84	(81-86)
2			77	(73-80)
3			72	(69-76)
4			68	(64-72)
5			66	(63-70)
By subgroup	Number of cases	Number of deaths	5-year survival (%)	95% confidence interval
All cases	879	321	66	(63-70)
Sex				
Male	488	191	63	(58-68)
Female	391	130	71	(65-76)
Age at diagnosis				
15-44	51	10	69	(52-81)
45-59	218	55	72	(65-78)
60-74	355	129	64	(58-69)
75+	255	127	67	(57-75)
Stage				
Localised	258	36	96	(90-100)
Regional	391	136	69	(64-75)
Distant	162	121	9	(5-16)
Unknown	68	28	63	(49-76)
Selected period				
1995-99			64	(60-69)
2000-04			69	(64-72)

Source: ACT Cancer Registry

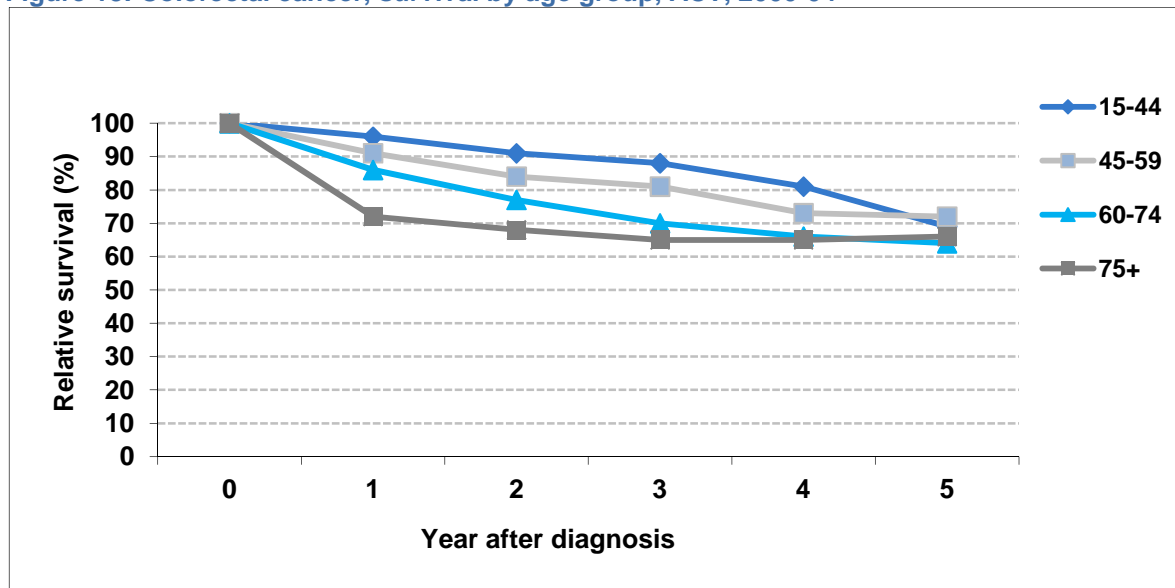
The 5-year survival for ACT residents was 66%. Females (71%) had a higher 5-year survival than males (63%) (Table 1). Localised disease had a substantially higher survival ratio (96%) compared to a disease with regional spread (69%). Older age at diagnosis showed lower survival. The 5-year survival ratio in more recent years (2000-04) was higher (69%), but not significantly higher, than in the preceding years 1995-99 (64%) (Figures 17-20).

Figure 17: Colorectal cancer, survival by sex, ACT, 2000-04



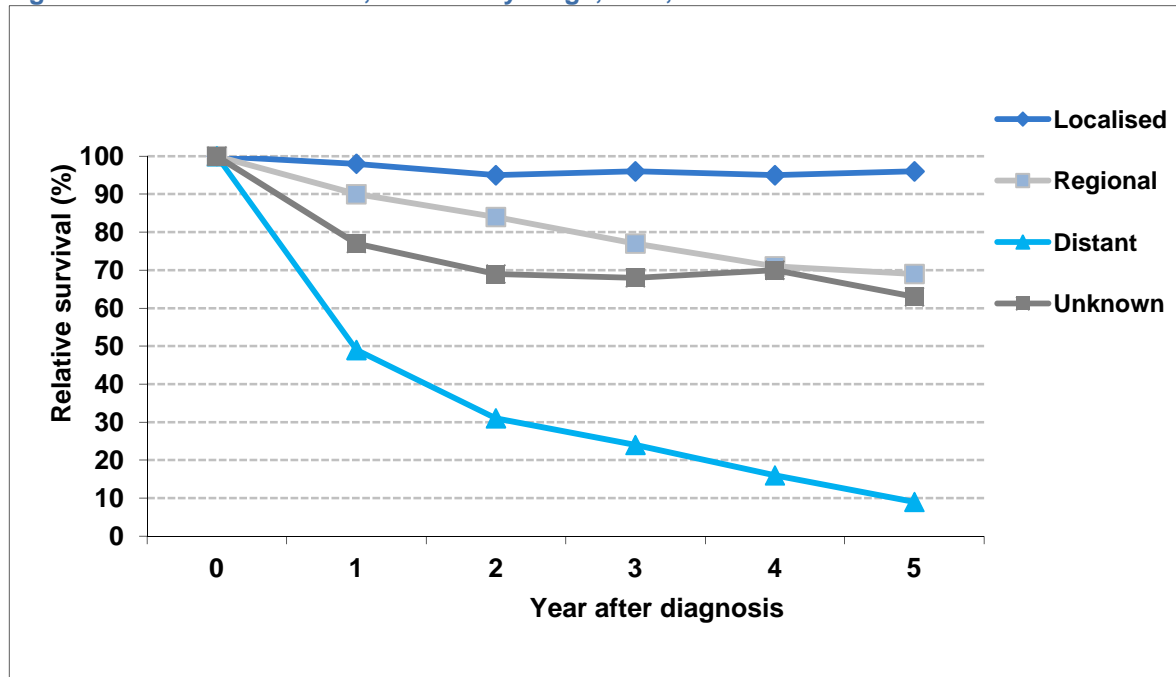
Source: ACT Cancer Registry

Figure 18: Colorectal cancer, survival by age group, ACT, 2000-04



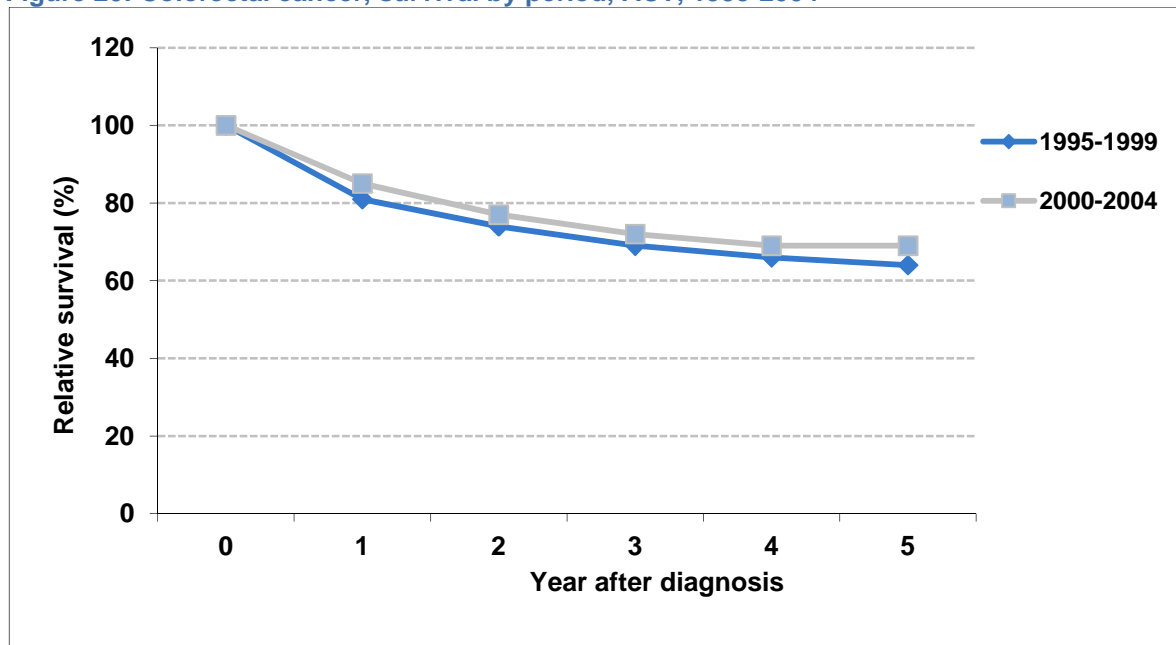
Source: ACT Cancer Registry

Figure 19: Colorectal cancer, survival by stage, ACT, 2000-04



Source: ACT Cancer Registry

Figure 20: Colorectal cancer, survival by period, ACT, 1995-2004



Source: ACT Cancer Registry

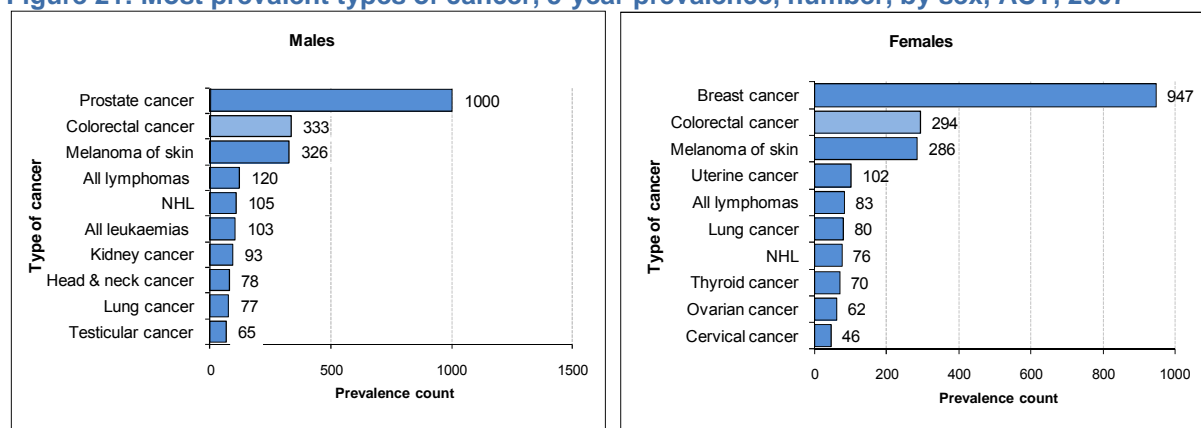
6. Prevalence

Cancer prevalence identifies people who are alive with a prior diagnosis of cancer at a point in time. Prevalence is often divided into subgroups based on health care requirements. Five year prevalence includes everyone who is alive five years after diagnosis, and includes persons who may still be undergoing treatment or have had a recurrence. Ten year prevalence may include persons who are considered to be cured. From a public health perspective, it is useful to estimate the number of persons living with cancer in the population, to identify the burden of disease and to influence health care planning in terms of allocation of resources and services.

As at the end of 2007, there were 333 males and 294 females (Figure 21) who were living in the ACT following a diagnosis of colorectal cancer within the previous five years; 571 males and 482 females within the previous ten years.

Colorectal cancer is the second most prevalent type of cancer in the ACT (Figure 22).

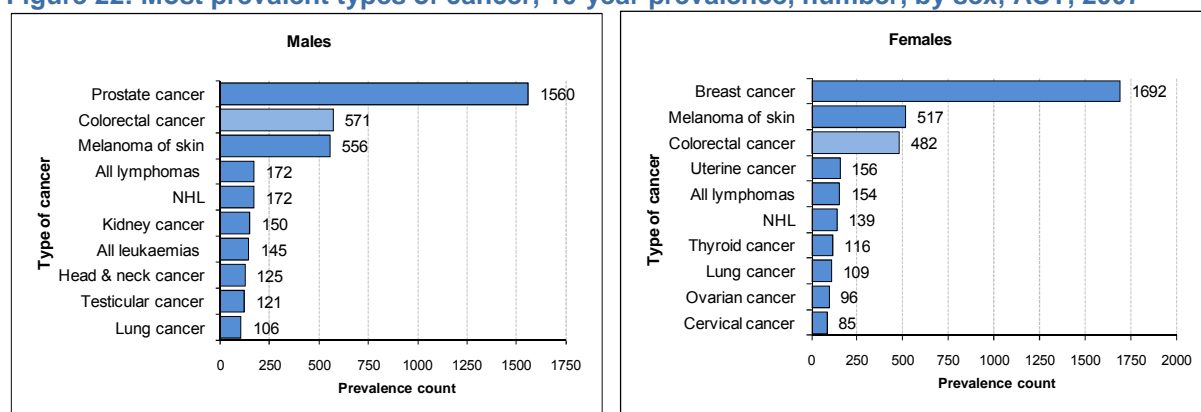
Figure 21: Most prevalent types of cancer, 5-year prevalence, number, by sex, ACT, 2007



Notes: Prevalence data were as at 31 December 2007; NHL Non-Hodgkin's lymphoma.

Source: ACT Cancer Registry

Figure 22: Most prevalent types of cancer, 10-year prevalence, number, by sex, ACT, 2007



Notes: Prevalence data were as at 31 December 2007; NHL Non-Hodgkin's lymphoma.

Source: ACT Cancer Registry

7. Screening

The National Bowel Cancer Screening Program began in late 2006 (Phase 1) and finished in December 2010. The goals of the program were:

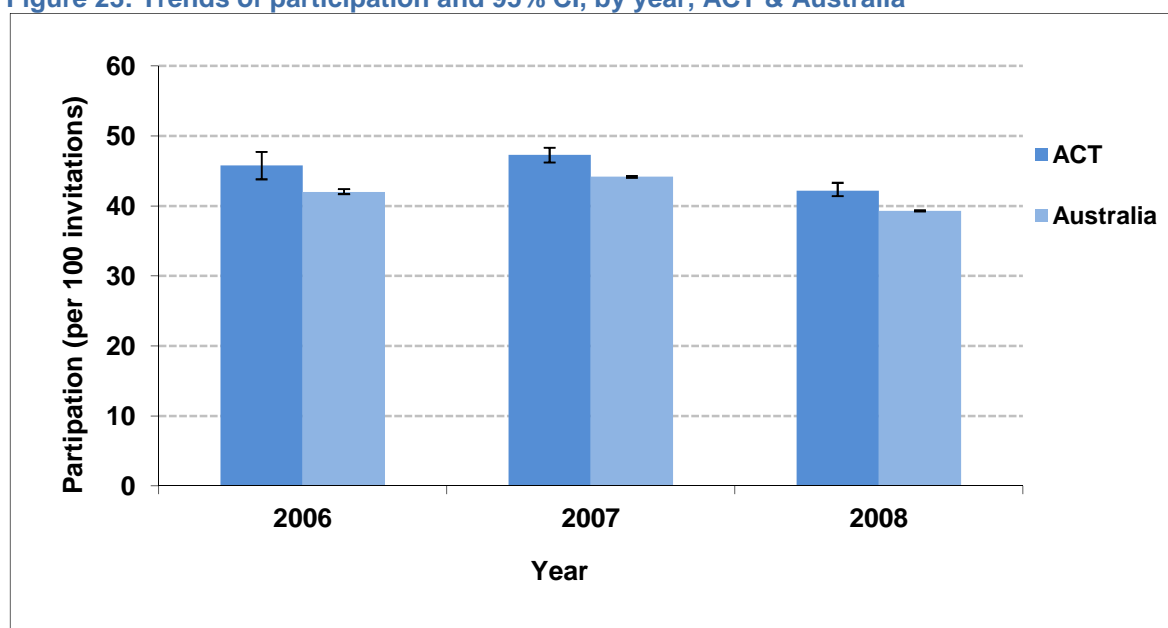
- to reduce the incidence of and mortality due to bowel cancer, through screening to detect abnormalities of the colon and rectum at a pre-cancerous stage; and
- where bowel cancer has developed, to detect cancers at an early stage to maximise the effectiveness of treatment.

Eligible participants received an invitation by mail to complete the screening test called the Faecal Occult Blood Test (FOBT) and mail it back to pathology laboratory for analysis. Eligible participants were people identified and invited to participate generally within four weeks of their 50th, 55th or 65th birthday. If the results was positive, the participants were followed up for further investigation by colonoscopy. The result from the colonoscopy was a definitive test to confirm bowel cancer or other lesions.

The second phase of the program commenced on 1 July 2008 and offered testing to people turning 50, 55 or 65 years of age between January 2008 and December 2010.

The participation proportion for the ACT was significantly higher than the rest of Australia during 2006-2008 (Figure 23).

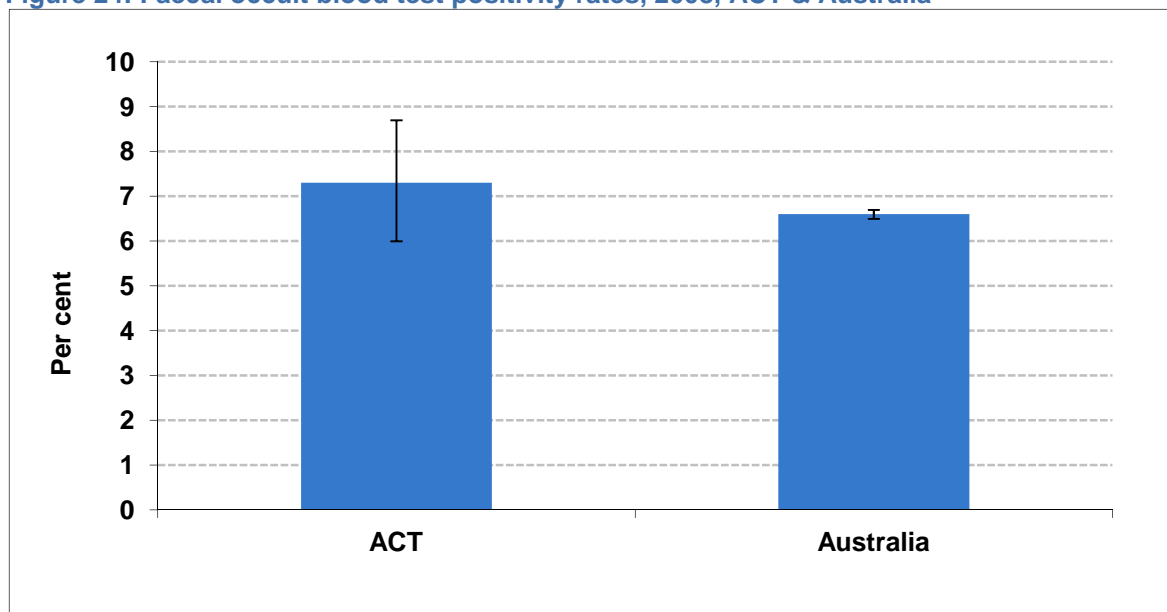
Figure 23: Trends of participation and 95% CI, by year, ACT & Australia



Note: CI= confidence interval.
Source: National Bowel Cancer Screening Program Register²

The FOBT positivity rate of the ACT was similar to Australia in 2008 (Figure 24).

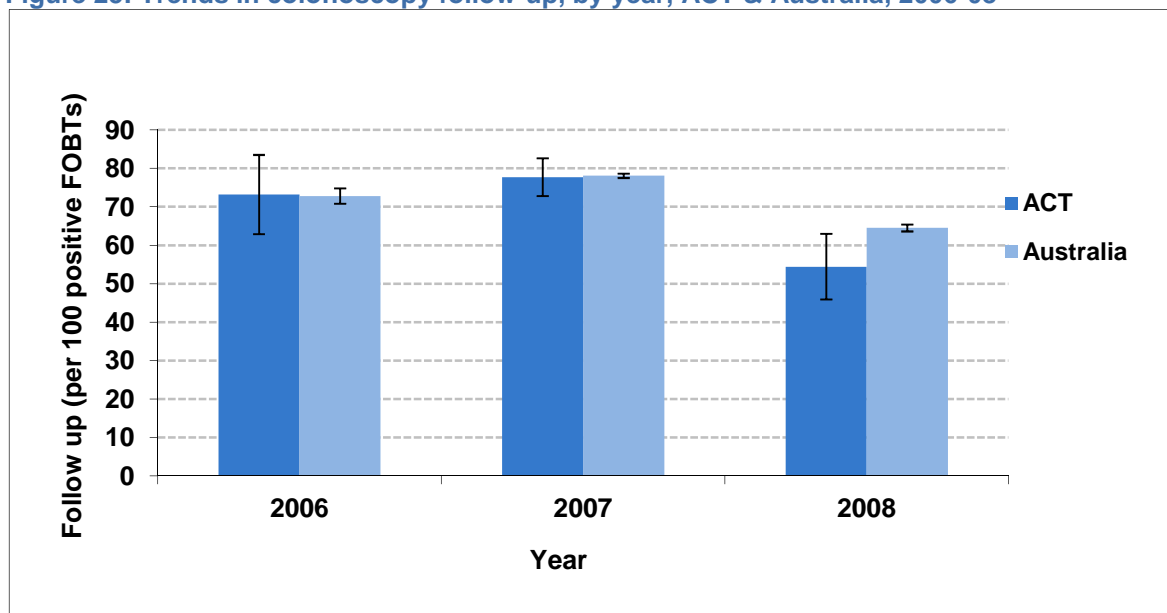
Figure 24: Faecal occult blood test positivity rates, 2008, ACT & Australia



Source: National Bowel Screening Program Register²
Notes: Rates equal the number of participants with positive FOBT results as a percentage of the total number of participants with valid results. A valid result was either positive or negative; inconclusive results were excluded.

The rate of colonoscopy follow-up for the ACT was similar to Australia in 2006-07, but lower (not significantly lower) than Australia in 2008.

Figure 25: Trends in colonoscopy follow-up, by year, ACT & Australia, 2006-08



Source: National Bowel Screening Program Register²
Note: Rates equal the number of people with a positive FOBT who underwent a colonoscopy as a proportion of the total number of people with positive FOBT results.

8. Risk factors

Many of the known risk factors for colorectal cancer are not easily modifiable. These include:

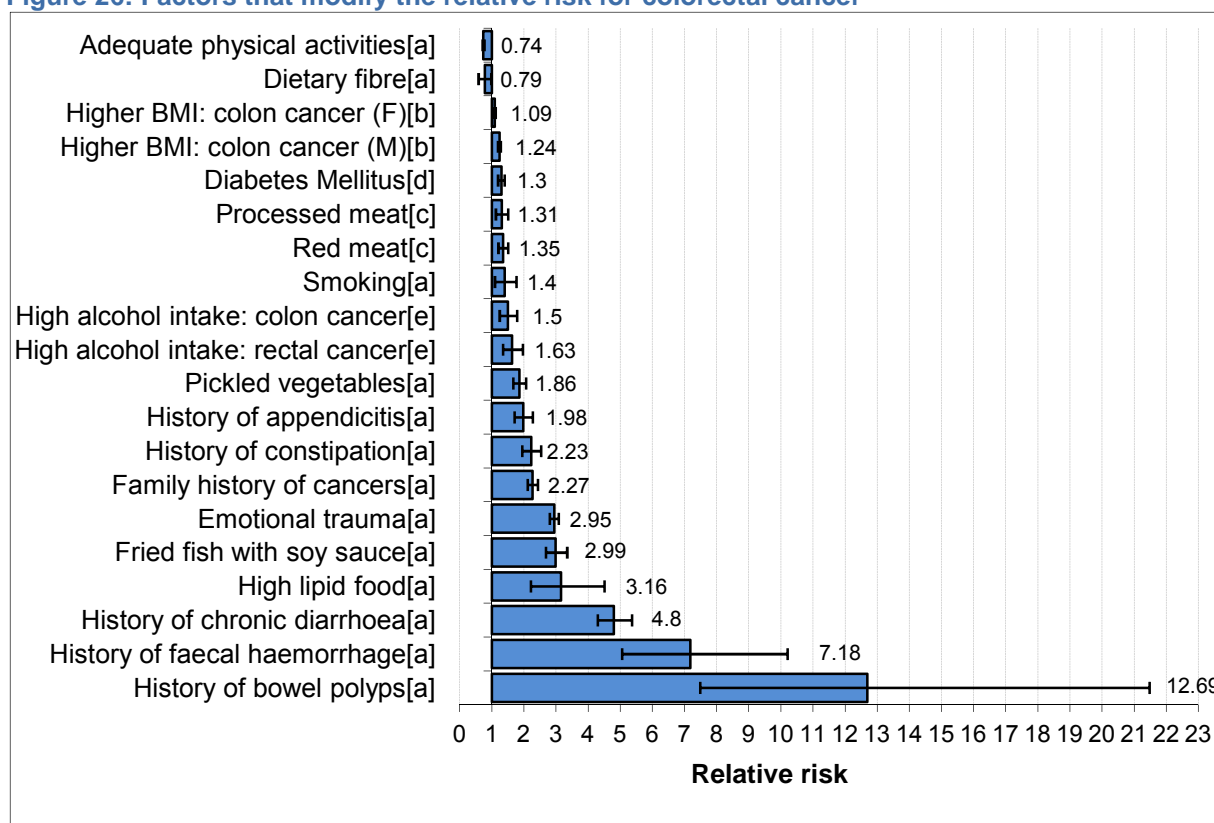
- Increasing age
- Family history of colorectal cancer
- Inherited diseases (e.g. familial adenomatous polyposis, hereditary non-polyposis coli)
- Inflammatory bowel diseases
- Diabetes mellitus

However, other risk factors related to life styles are modifiable. These include:

- Lack of exercise
- Obesity
- Excessive alcohol consumption
- Tobacco smoking
- Unhealthy diet

Figure 26 shows the relative risk for colorectal cancer for the various risk factors. It can be seen that history of bowel polyps or faecal haemorrhage have by far the highest relative risk of all the risk factors. Although most of the modifiable risk factors generate smaller relative risk, they are nevertheless important to note in any program to reduce the incidence of colorectal cancer.

Figure 26: Factors that modify the relative risk for colorectal cancer



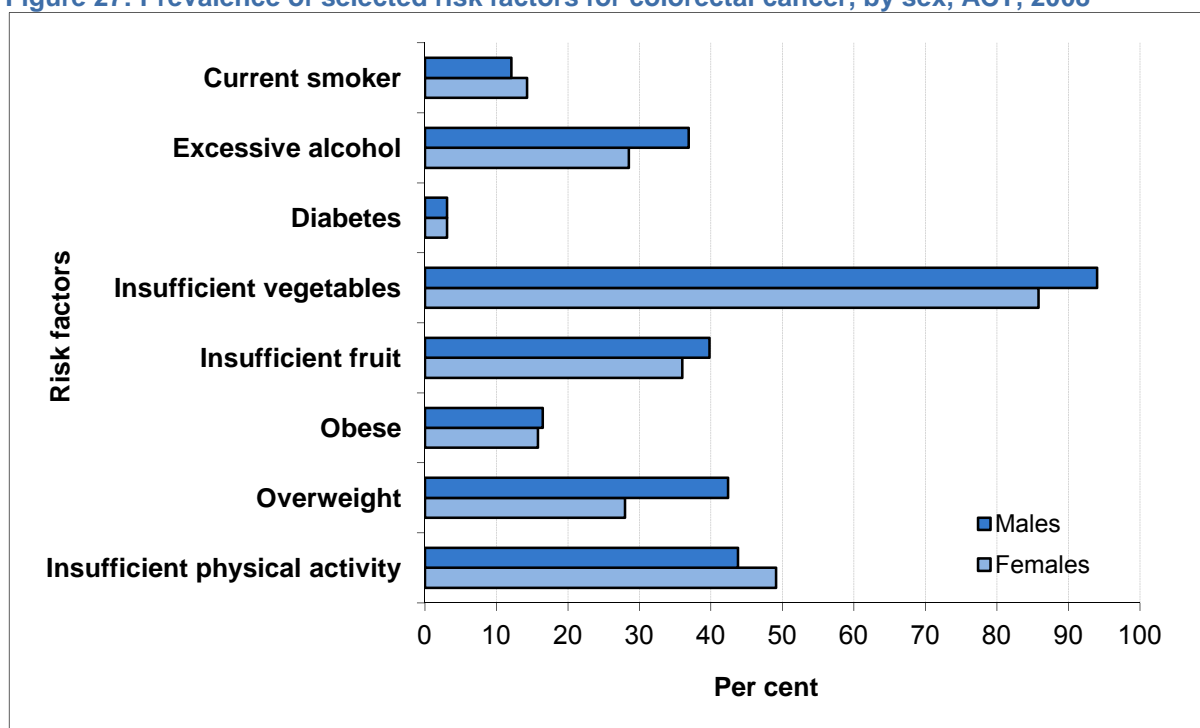
Notes: Relative risk is defined as the risk of having colorectal cancer if an individual is exposed to the risk factor compared to the risk of having colorectal cancer if an individual is not exposed to the risk factor. Thus, the higher the relative risk, greater is the association between the risk factor and colorectal cancer. The 95% confidence interval is indicated by the H bar.

Source: a³; b⁴; c⁷; d⁵; e⁶ (See references)

8.1. Prevalence of selected risk factors for colorectal cancer in ACT

According to the self-reported data from the ACT General Health Survey, 2008⁸, a greater proportion of males than females in ACT engaged in health risk behaviour that may promote the development of colorectal cancer, with the exception of smoking and insufficient physical activity. The majority of ACT residents did not eat the recommended amounts (2 serves of fruits and 5 serves of vegetables per day) of fruits (males: 40%; females: 36%) and vegetables (males: 94%; females: 86%). A large proportion of ACT residents was either overweight or obese; had insufficient physical activity and consumed excessive amount of alcohol.

Figure 27: Prevalence of selected risk factors for colorectal cancer, by sex, ACT, 2008



Source: ACT General Health Survey, 2008⁸.

9. Discussion

Colorectal cancer is a major public health issue in the ACT and Australia. Colorectal cancer was the second most common cancer in both males and females in the ACT accounting for 13% of cancers in 2004-08. It was the fourth most common cause of death among ACT residents during 2003-07.

The high incidence of colorectal cancer over time is in part a reflection of the prevalence of risk factors related to life-styles. A large proportion of ACT residents, males in particular, were overweight or obese; not participating in sufficient physical activities, not eating sufficient fruits and vegetables and consuming an excessive amount of alcohol. This is likely to at least partially account for the higher incidence rate observed for males between 1985 and 2008.

Mortality from colorectal cancer has decreased significantly over time. The decrease in mortality rate was observed in both males and females. This decrease is a reflection of improving treatment for colorectal cancer in the last two decades in the ACT. By the end of 2007, there were 333 males and 294 females in the ACT who had a diagnosis of colorectal cancer within the previous five years. This number of people included those who may still be undergoing cancer treatment or have had a recurrence.

The ACT had a high participation rate in the National Bowel Cancer Screening Program. Since the program aims to detect cancers at an early stage, this is an encouraging result. With early detection of cancer, there is better survival at individual level and lower mortality at the population level. However, it may be too early to detect the impact of the screening program as Phase 2 only started in 2008.

10. Statistical definitions and methodology

This report contains the number of new cases and deaths, and age-specific, crude, cumulative, and age-standardised incidence and mortality rates of ACT residents diagnosed with cancer and in particular, colorectal cancer. They are based on registrations completed by 31 December 2010.

Incidence

Cancer incidence is defined as the number of new cases of cancer in a population during a specific period. The incidence data in this report refer to the number of primary cancers first diagnosed between 1 January 2004 and 31 December 2008.

Median age

Median age at diagnosis is the middle value, i.e. 50 per cent of cancer cases are diagnosed at an older age and 50 per cent are diagnosed at a younger age compared to the median age. The interquartile range represents the age at which 25 per cent of the cases are above and 25 per cent below the median age.

Mortality

Cancer mortality refers to deaths from cancer in a given population occurring in a specified period. These cancers may have been diagnosed during or before the period in question. The mortality data in this report are based on cancer deaths between 2004 and 2008 of people who developed their cancer while residing in the ACT. The death may have occurred outside the ACT. Cases for which a death certificate was the only source of notification (1.4%) and those diagnosed at post mortem (0.1%) are included.

Crude rates (CR)

The crude incidence rate is calculated as the number of new cases of cancer divided by the population at risk in a specified time period. The crude mortality rate substitutes deaths for new cancer cases in this calculation. Both are conventionally expressed as annual rates per 100,000 population. The Australian Bureau of Statistics (ABS) supplied the estimated ACT population by age and sex for each year as at 30 June between 2004 and 2008.

In this report, average annual cancer rates over the period 2004-08 were provided, rather than single year rates. This is mainly because of the relatively small number of cancer cases in the ACT, particularly deaths, from cancers of most sites. Such a situation results in rates which are unreliable in that they may vary widely from year to year. These fluctuations in rates are not meaningful, merely reflecting a difference due to a few cases. Use of combined data from five years provides a larger total number of cases and a more accurate estimate of the true rate.

Age-specific rates

Age-specific rates are calculated by dividing the number of cases occurring in each specified five-year age group (and sex) by the corresponding population in the same age group (and sex) and are expressed as an annual rate per 100,000 population.

Age-standardised rates (ASR)

Rates are adjusted for age to facilitate comparisons between populations that have different age structures, eg. between youthful and ageing communities. In this report, direct standardisation is used in which age-specific rates are used to calculate the number of cases that would have occurred if the population had the same age distribution as the Australian Standard Population 2001. This effectively removes the influence of age structure on the summary rate, which is described as the age-standardised rate. The method can be used for both incidence and mortality calculations.

Cumulative rates

A cumulative rate is a directly standardised rate with equal weights in each age group of interest and zero weight otherwise and is calculated from the age-specific rates. In this report, ages 0-84 years are used as an approximation of an average lifetime. Cumulative rates are often expressed as percentages (rates per 100).

Cumulative risk

Cumulative risk is a more exact measure of risk, which takes account of the sequential removal, from the population at risk, of people who are diagnosed with (for incidence) or die of the disease. It can be calculated from the cumulative rate. It is expressed in this report as a risk of "one in n". It is calculated from the age-specific rates (incidence and death) from birth to 84 years.

Three-year moving average

The 3-year moving average was calculated by summing the age-standardised incidence or mortality rates for the 3-year period centred on the year of interest and dividing the total by three. For the first and last years in each series the rates were averaged over two years.

Prevalence

Prevalence is a useful measurement that provides health care planners and cancer support personnel with the number of people who remain alive following a diagnosis of cancer.

Point prevalence is the proportion of existing cases (old and new) in a population at a single point in time. Point prevalence is often referred to as prevalence. This is different from incidence which is the number of new cases in a given period of time, usually a calendar year.

Prevalence is affected by both the number of new cases with cancer (incidence) and the length of time patients survive after being diagnosed. For example, even though two types of cancer might have similar incidence, if cancer A has low survival rates and cancer B has higher survival rates, then the prevalence of cancer B is expected to be higher.

In this report “limited duration of prevalence”, which counts cases who remain alive at a given time point (i.e. 31 December 2007) as prevalent when they were diagnosed within a specific time period is presented. Limited duration prevalence for major cancers are presented for 5 and 10-year time periods. The time point 31 December 2007 was chosen as the cut point for prevalence because it was the most updated version at the time of writing this report with matching of the ACT cases to the National Death Index.

Joinpoint analysis

The joinpoint regression method is similar to the least square regression method. The joinpoint method evaluates changing trends over successive segments over time. A joinpoint is the point at which the linear segment changes significantly.

The program starts with the assumption of constant change over time (i.e. no joinpoint). Up to three joinpoints were tested in each model, depending on the number of years of data available and the stability of the yearly estimates. The trend line was tested against the statistical significance using a Monte Carlo Permutation method.

The average annual percentage change (AAPC) is the average yearly increase or decrease in incidence or mortality trends over the specified period, expressed as a percentage. Positive annual percentage change (APC) values indicate an increasing trend whilst negative APC values indicate a decreasing trend. A trend is taken to be statistically significant if the 95% confidence interval does not include zero.

APC values in this report were calculated using a statistical method called joinpoint regression analysis or segmented regression, with software, Joinpoint Regression Program 3.3.1, developed by the National Cancer Institute of the USA⁹.

11. References

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