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Changing trends in colorectal cancer: possible cause and clinical implications

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ABSTRACT

OBJECTIVES: The aims of this study were to determine whether pattern of patients presenting with colorectal cancer (CRC) in the last few years differs significantly from that previously reported in Australia, and to relate the trends, if present, to use of hormone replacement therapy (HRT). METHODS: We examined demographic and pathological characteristics of 145 consecutive CRC patients (65 females) treated in our institution in calendar years 2006-2007. Comparisons were made with data on 12536 CRC patients obtained from the Australian Association on Cancer Registries (AACR) for the year 2003, most recent available. Prescribing data for HRT were obtained from the Australian Commonwealth Department of Health and Ageing. RESULTS: The distribution of colon, sigmoid and rectal cancers in our series was 40%, 24.8% and 35.2%, respectively, which differs significantly from 65%, 8.1% and 26.9% in the AACR data ($p < 0.01$). Our cohort was significantly younger (65.4 ± 12.1 vs. 69.5 ± 12.3 years), especially females (63.0 ± 12.7 vs. 70.3 ± 13.0 years; $p < 0.001$). The proportion of female patients aged < 55 and < 60 years was significantly higher (30.8% vs. 13.8% and 41.5% vs. 21.4%, respectively). Younger patients have more aggressive and advanced cancers. In Australia HRT use declined since 2001 and fell by a half in 2006. CONCLUSIONS: In the changing CRC pattern of greatest concern is a significantly higher proportion of younger patients, especially females, with higher prevalence of more advanced and aggressive cancers, coincident with decreased prescribing of HRT. These findings may have important implications for refining screening and preventive strategies and on demand for radiotherapy services.

Keywords: Colorectal Cancer; Age; Gender; Hormone Replacement Therapy; Trends

1. INTRODUCTION

Colorectal cancer (CRC) is the most prevalent non-skin malignancy and second highest cause of cancer-related death in Australia [1] as in other industrialized countries. The incidence and mortality increase with age and the risk of being diagnosed with CRC by age 85 years is one in 10 for males and one in 14 for females [1]. In the last two decades a decline in incidence and mortality rates for CRC has been observed in most developed countries including Australia [2-9]. The reasons for this trend may include risk factors modification, introduction of screening and improvements in medical intervention.

The characteristics of CRC vary significantly with age, gender, race/ethnicity and region of residence [7,10-12]. The causes for these differences, genetic, environmental or acquired, are not fully understood. Numerous epidemiological studies have suggested a protective effect of estrogens (alone or in combination with progestins) against CRC [13-18]. A meta-analysis of 18 observational studies of CRC and use of hormone replacement therapy (HRT) indicated a 34% reduction among current users and a 20% reduction among ever users [19]. Similar data were reported in a large randomised controlled trial [20]. However, since the Women's Health Initiative (WHI) hormone trial demonstrated the risks of HRT (coronary heart disease, stroke, breast cancer, venous thromboembolism, cholecystitis), a sharp decline in the use of HRT has been seen over the last few years [21]. No study to date has addressed possible effects of reduced HRT use on CRC trends.

In Australia, following a pilot program, national CRC screening program for people between 55 and 74 years of age is currently being phased in. However, the evidence in relation to target age is insufficient.

Better understanding of risk factors and regional trends, especially in relation to age, gender and anatomical site may prove invaluable in fine-tuning screening, providing better services and, perhaps, contribute to development of new preventative strategies. The purposes of the present study were 1) to determine whether pattern of patients presented with CRC to our institution in the last 2 years differs significantly from that previously reported in Australia in regard to age, gender, anatomical site, histopathology and TNM stage, and 2) to relate the trends, if present, to use of HRT.

2. METHODS

Study population consisted of 145 consecutive CRC patients (age ranged from 34 to 85 years, mean 65.4 ± 12.13 years) treated in calendar years 2006 and 2007 in the Dandenong Hospital, a major public teaching hospital. The patients were admitted from a catchment area of approximately 360,000 inhabitants. The information collected included patient demographics, stage, grade and anatomical site of the cancer. The sites of CRC were determined from the surgical description and the pathology report and classified according to the International Statistical Classification of Diseases (ICD) 10th revision. In order to compare results with previous reports three subsites were defined and analyzed: colon (the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure and descending colon), sigmoid colon (sigmoid and rectosigmoid junction) and rectum. We used a broad definition to categorize the proximal (descending colon and above), and distal segments of colon because current data indicate that subsites within sigmoid colon have characteristics similar to rectal-type cancers rather than proximal-colon cancers.

TNM staging was based on the operative findings and the histopathological report. Histological grade was recorded as well, moderately, or poorly differentiated.

Comparison data for Australia-wide patterns of CRC were obtained from the Australian Association of Cancer Registries (AACR) for the year 2003, most recent available. These included data on 12,536 CRC patients analyzed on the same lines as ours. Unfortunately, AACR does not provide data concerning TNM staging. Therefore, such analysis was performed for our study population only.

To examine trends in HRT use data were obtained from the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme databases (Medicare Australia PBS Statistics), as well as from the annual Australian statistics on medicines reports. The latter use a combination of PBS data and survey data from a sample of community pharmacies.

For statistical evaluation data were presented as a number of cases and percentages with 95% confidence intervals (CI), chi-square and Fisher exact test were used for statistical analysis of these. Quantitative normally distributed data were expressed as means and standard deviation (SD) and Student's t-test was used for comparing mean values. Two-tailed P value was considered significantly at < 0.05 level.

3. RESULTS

Of 145 patients with CRC admitted to our hospital in the 2 year period there were 65 (44.8%) females with a mean age of 63.0 ± 12.7 years and 80 (55.2%) males with a mean age of 67.3 ± 11.4 years. Colon cancer was diagnosed in 58 patients (32 females), sigmoid in 36 (16 females) and rectal in 51 (17 females). In our series there was a more distal distribution of CRC comparing with that seen previously in the Australian population: the proportion of rectal (35.2% vs 26.9%, $p = 0.032$) and sigmoid cancers (24.8% vs 8.1%; $p = 0.003$) was significantly higher and the proportion of colon cancers (40% vs 65%, $p = 0.001$) was significantly lower. The distal colon (sigmoid and rectal) was the most common site of carcinomas contributing 55.9% of all cases (50.8% in females and 67.5% in males). The ratio of proximal to distal cancers was 0.67 in our series and 1.85 in the previous report.

The age-distribution pattern was similar in both studied periods with CRC rare before the age of 30, significant increase after the age of 45 until 75-79 and decline thereafter. But the 2006-2007 data revealed a marked shift to the younger age most pronounced in females. Our cohort overall was on average 4 years younger ($p = 0.001$), and the females were 7.3 years younger than previously reported ($p < 0.001$) (**Table 1**). The difference was statistically significant in females with colon and rectal cancers, while no differences were observed in males for any cancer site. In our series females with rectal cancer were the youngest, they were on average 7.9 years younger than previously reported and 3.8 years younger than males with rectal cancer.

The total male/female (M/F) ratio in our series was the same as reported previously (1.23 and 1.21, respectively). As indicated in **Table 1**, in both studied periods the M/F ratio increased markedly from colon through the rectum site. However, our series demonstrated that, comparing with the previously described, the M/F ratio was significantly lower in colon cancer patients (0.81 vs

Table 1. Comparison of mean age (years ± SD) of CRC patients in two studied periods by gender and site distribution of carcinomas.

Period	Gender	All Patients	Cancer Site		
			Colon	Sigmoid	Rectal
2003	Females	70.3 ±13.01	71.4 ± 12.56	67.7 ± 13.09	67.8 ± 13.83
2006-2007		63.0 ± 12.68***	63.9 ± 14.16***	64.4 ± 12.63	59.9 ± 9.54***
2003-2004	Males	68.8 ± 11.56	69.9 ± 11.27	67.7 ± 10.92	66.9 ± 11.42
2006-2007		67.3 ± 11.38	72.1 ± 9.37	67.3 ± 9.24	63.7 ± 12.74
2003	Both Genders	69.5 ± 12.26	70.6 ± 11.97	67.7 ± 11.91	67.2 ± 12.68
2006-2007		65.4 ± 12.13***	67.6 ± 12.82*	66.0 ± 10.81	62.4 ± 11.81***
2003	Male/Female Ratio	1.21	1.06	1.30	1.64
2006-2007		1.23	0.81	1.25	2.00

*** $p < 0.001$, * $p < 0.05$

1.06) and higher in rectal cancer patients (2.00 vs 1.64), indicating that the proportion of males with distal cancers is increasing. The ratio of proximal to distal cancers in females was 0.97 in our series and 2.30 in the previous report and in males 0.48 and 1.57 respectively, again suggesting a pronounced shift to distal cancer sites especially in males.

In our cohort, patients < 50 years of age comprised 12.4% (18.5% females and 7.5% males), < 55 years of age 20.0% (30.8% and 11.3% respectively), < 60 years of age 33.1% (41.5% and 26.3% respectively). In 2003 the corresponding figures were 6.9% (7.8% and 6.2%), 12.9% (13.8% and 12.3%) and 21.4% (21.2% and 21.7%). The proportions of younger patients with CRC by gender and cancer site are given in **Figure 1**. In the recent series the proportion of patients with CRC younger than 50, 55 or 60 years of age was significantly higher than previously reported due to a 2-fold increase in the proportion of younger females with cancers at all sites except sigmoid. In our cohort, among females with colon cancer 31.3% were aged < 55 years and 37.5% were aged < 60 years. Corresponding figures in the previous report were 11.6% and 17.9%. Similarly in our series, among females with rectal cancer 35.3% were < 55 years of age and 64.7% were < 60 years of age, while previously this has been observed only on 19.1% and 28.9, respectively.

The prevalence of advanced clinicopathological features of CRC in our younger patients is presented in **Table 2**. A significant proportion of patients with locally advanced T3 and T4 cancers were younger than 55 years of age (25% females and 13.3% males). Importantly, most of patients < 55 years of age were in T3 and T4 categories (12 of 20 females and 8 of 9 men). This age group contributed to 1/3 of all females and 1/5 of all males with lymph nodes metastasis and/or poor differentiation. The frequency of node metastasis was significantly higher in females than in males. ($p = 0.018$). Subjects younger than 60 years of age comprised from 1/3 to about 1/2 of all patients with advanced and/or unfavorable CRC.

Figure 2 presents the proportion of females with CRC in 5 year age groups in the recent series and in Australia in 2000 and 2003. The age-distribution patterns in 2000 and 2003 were similar, while in 2006-2007 there was a significant increase in proportion of females aged 45 to 59. This age group comprises the majority of women who use HRT.

Figure 3 displays the combined number of prescriptions for Premarin and Depo-premarin (most frequently prescribed HRT drugs) in Australia and Victoria over a 10-year period (financial years 1997/8-2006/7). The number of prescriptions peaked in 1999 and has declined since 2001. In Australia the total number of prescriptions for these drugs dropped in 2002 by 30.7% compared with the previous year and by 54.1% in 2006; in Victoria the corresponding figures were 32.4% and 55.4% respectively. These data are comparable with 40% drop in the number of total HRT prescriptions among conces-

Table 2. Proportion (%, 95% confidence interval) of younger subjects among patients with advanced CRC (2006-2007).

Age (years)	Total	Females	Males
	T3/T4 stage		
< 55	**18.5** (11.7-27.1)	**25.0** (13.6-39.6)	**13.3** (5.9-24.6)
< 60	**32.4** (23.7-42.1)	**35.4** (22.2-50.5)	**30.0** (18.8-43.2)
	N1/N2		
< 55	**25.0** (14.4-38.4)	**34.6** (17.2-55.7)	**16.7** (5.6-34.7)
< 60	**35.7** (23.4-49.6)	**42.3** (23.4-63.1)	**30.0** (14.7-49.4)
	Poor Differentiation		
< 55	**29.0** (14.2-48.0)	**33.3** (13.3-59.0)	**23.1** (5.0-53.8)
< 60	**38.7** (21.8-57.8)	**44.4** (21.5-69.2)	**30.8** (9.1-61.4)

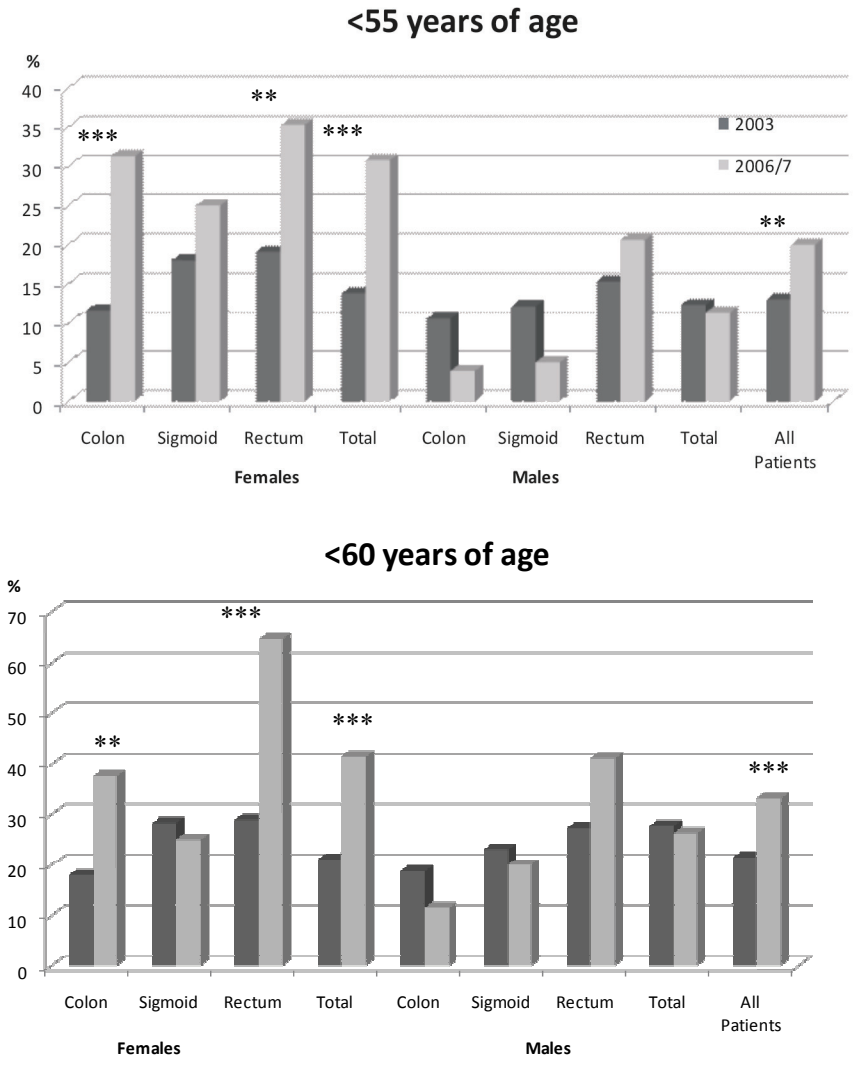

Figure 1. Proportion (%) of younger patients with CRC in two study periods by gender and cancer site. *** $p < 0.001$, ** $p < 0.01$.

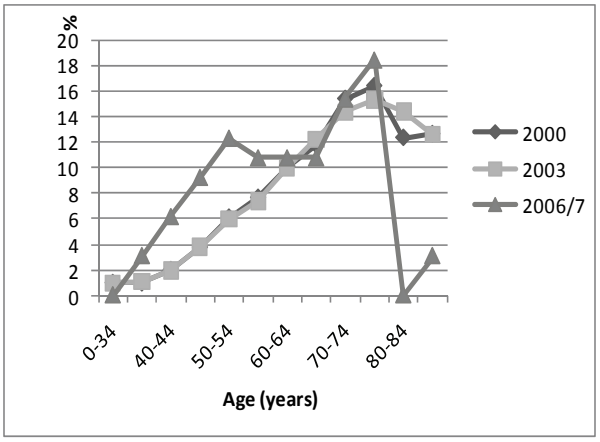

Figure 2. Age-distribution patterns of CRC in females in Australia in 2000 and 2003 and in our series 2006-2007.

Figure 3. Prescriptions for Premarin and Depo-provera (combined data) in Australia and Victoria, 1997-2006.

sion cardholders in Australia from 2001 to 2003. In this period a similar decline was observed in prescriptions for estrogen-only preparations (39% decrease), and combined estrogen-progestogen preparations (–41%) [22].

4. DISCUSSION

Our study indicates a change in pattern of CRC occurrence in 2006-2007. Compared with Australian data for 2003 our experience is of more distal cancers, greater proportion of younger patients, especially females, with high prevalence of more advanced and aggressive tumors. Several potential explanations for the changes in CRC characteristics observed in our study should be considered.

Cancers of proximal and distal colon might differ in their genetic nature, oncofetal antigen expression and evolve through different pathways and may be associated with distinct risk factors [6,23-29]. Proximal tumors compared to distal ones have a higher proportion of DNA microsatellite instability cancers, are more common in women and older patients. Risk factors for these include high intake of red meat and animal fat, low consumption of vegetables and fiber, sedentary life style, obesity and lower socioeconomic status. Alcohol consumption and smoking [30-32], use of aspirin and non-steroidal anti-inflammatory drugs (NSAID) [33-35] and especially postmenopausal HRT use [15,19,20,36-40] have also an important influence on CRC risk. Although we cannot fully evaluate the possible effects of all the mentioned risk factors for CRC, it seems unlikely that considerable changes in dietary and lifestyle habits occurred in our population between 2003 and 2006-2007. However, one variable which may be relevant, namely, a substantial reduction in HRT use, is obvious. In Australia and Victoria after 2001 prescriptions of Premarin and Depo-provera fell by a third in 2002 and by a half in 2006. A similar rapid and substantial drop in total HRT prescriptions from 2001 to 2003 was reported in Australia and New Zealand [22]. Age and gender-related changes in anatomical subsite CRC distribution observed in our study may be attributed, at least in part, to reduced HRT use after 2001. If hormonal factors protect against CRC then the reduced use of HRT should be accompanied by an increase in colon cancers in women during early postmenopausal period, as HRT use is associated mainly with reduced risk of colon cancer [14,15,20, 37,41]. Our experience is consistent with such expectations.

This study comparing with previous Australian data clearly demonstrated three points: only females with CRC were significantly younger (on average 7.5 years), there was a substantial increase in proportion of females aged 45 to 59 years who comprise the majority of HRT users and the male predominance in colon cancer was reversed (M/F ratio for colon cancer was 0.81 in 2006-2007 whereas 1.06 in 2003). Notably, the majority of our younger patients had aggressive and advanced CRC. Previous studies indicated that decrease in estrogen level after menopause increases the risk of a colon cancer with poorer differentiation [11,42]. Our findings are in line with the assumption of an approximate 3-5 year time lag between decrease in HRT use and its impact on CRC incidence rate [21,43,44]. In the Women's Health Initiative (WHI) trial the 38% lower risk of CRC observed in women prescribed HRT during the trial phase disappeared within 3 years of discontinuing HRT [43].

Numerous epidemiological and experimental studies suggested a favorable influence of HRT on CRC risk. It was estimated that estrogens alone or in combination with progestins reduce colon risk by 20-44% in postmenopausal women, and the duration of HRT did not influence risk estimates [19-21]. In the present study a sharp drop in the HRT use after 2001 was associated with 20.1% increase in the proportion of females < 60 years of age with CRC compared to the 2003 data. If this association is causal a further increase in CRC female patients should be expected. Of interest, the substantial decrease in HRT use was associated with a decline of breast cancer incidence in Australia, US and other countries [22,45,46]. The protective effects of estrogen on colonic carcinogenesis are mediated predominately through estrogen receptor β (ER-β) involving both genomic and non-genomic mechanisms [40]. ER-β-knockout mice demonstrate hyperproliferation, loss of differentiation and disordered apoptosis of colonic mucosa, as well as disorganization of mucin localization, reduction in the number of hemidesmosomes and loss of tight junctions of colonic epithelium [47], indicating that ER-β plays a pivotal role in maintenance of cellular homeostasis in the colon. ER-β is the dominant receptor in human colonic mucosa and seems to be essential for preventing malignant transformation of colonic epithelial cells. A significant reduction of ER-β expression has been shown in colon adenocarcinoma cells and this correlated with tumor dedifferentiation, stage and grade [42,48,49]. Moreover, in the pre-malignant phase of colon carcinogenesis ER-β expression is also reduced and inversely correlates with increase of proliferative activity in the adenomatous tissue [50]. It has been shown previously that methylation associated inactivation of estrogen receptor gene in ageing colorectal mucosa is one of the earliest events predisposing to cancerogenesis [51]. Other postulated mechanisms by which HRT use might reduce CRC risk include the influence of estrogens on bile acids [52,53], insulin and glucose control [54].

Our findings may have important practical implications for present and future screening strategies, treatment and prevention of CRC. Early diagnosis of CRC could improve survival. Currently CRC screening in Australia is advocated for people aged 55 and older. However, in our series patients younger than 55 years comprise 20% (females 31%, males 11%), suggesting that the optimal cut-off age for screening needs to be reviewed. Although we observed a distal shift of CRCs, in 40% of our patients (in 49.8% of females and in 30.6% of males) the cancers were located above the sigmoid colon. These tumors will be missed if sigmoidoscopy (not total colonoscopy) is chosen as the screening technique. The significant and rising number of rectal cancers (35.2% in total, 26.2% in females and 42.5% in males) is likely to increase demand for radiotherapy services. The observed association between the changing age and subsite patterns of CRC in females and the drop in HRT use in the context of current data on estrogen effects on growth, differentiation and functioning of epithelial cells in the colon and the protective role of estrogen in CRC may stimulate research of novel preventive and therapeutic approaches such as development of selective ER-β agonists. At present, the well established risks of traditional HRT [21] preclude its use to reduce the CRC in postmenopausal women [20]. However consumption of soy products and dietary fiber which are high in phyto-estrogens demonstrate a protective effect in CRC [55,56] and are not associated with breast cancer [57]. Of note, the re-analysis of the WHI data showed that women who started estrogen therapy at the age of 50-59 years and continued it for 6-7 years did not have an increased risk of coronary heart disease [58],and have a decreased risk of early-stage breast cancer and a decreased risk of ductal carcinomas when compared with placebo treated women, although the risk of stroke in the estrogen group was non-significantly elevated [59]. These data together with significantly decreased incidence of colon cancer and fractures with long-term HRT use indicate the potential benefits of HRT. However, additional large controlled studies are needed to find definitive criteria for HRT use—time of initiation (? menopause) and duration (? 5-6 years) of therapy—to have beneficial effects on women's health, including protection against CRC and to avoid adverse effect.

Some limitations of this study warrant consideration. Our study was a single hospital-based. We were not able to calculate true incidence rates and therefore the comparisons with previous report were performed using proportions of CRC patients in age and subsite categories. The observation that sharp decrease in HRT use was followed by changes in CRC patterns in females does not establish causal relationship between the two, but provides a logical explanation and is of importance to public health.

5. CONCLUSIONS

Our series of CRCs in 2006-2007 show important age-, gender- and subsite-related changed in CRC patterns compared with those seen in the Australian population previously (2003). Of greatest concern is a significantly higher proportion of patients aged < 55 and < 60 years of age (20% and 33% respectively), especially females (31% and 41.5%). Furthermore, there were more female patients with colon cancer and younger patients were more likely to have more advanced and aggressive cancers. These findings seem to be temporally, and possibly causatively, related to decrease in HRT use and may have significant implications for effective screening strategies, provision of radiotherapy services and further research in CRC pathogenesis and prevention.

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