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Age, sex and the risk of grade-specific second primary colorectal cancer: Evidence for the protective effect of female hormone

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ARTICLE INFO

Article history:
Received 3 April 2007
Received in revised form 11 May 2007
Accepted 18 May 2007
Available online 2 July 2007

Keywords:
Female
Male
Colorectal neoplasm
SEER program
Oestrogen receptors
Epidemiology

ABSTRACT

Aim: To investigate the interaction effects of age and sex on the risk of grade-specific second primary colorectal cancer (SPCRC).

Method: This is a retrospective cohort study, using registry data covering the period 1973–2003 from the SEER program, National Cancer Institute. The sex-age-specific incidence rates of Grade 1, Grade 2 and Grade 3 second primary colorectal cancer (SPCRC) were calculated. Poisson regression models were used to estimate the interaction effects between sex and age.

Results: The sex-age-specific incidence rates of Grade 1, Grade 2, and Grade 3 second primary colorectal cancer (SPCRC) increased gradually with age, especially in females. There was a significant interaction effect between sex and age on the risk of Grade 3 second primary colon cancer.

Conclusion: Decrease in female hormone level since menopausal age may increase the risk of a second primary colon cancer, especially a cancer with poorer differentiation.

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1. Introduction

Both males and females diagnosed with a primary colorectal cancer are at risk of being diagnosed with a second primary colorectal cancer.[1] A second primary colorectal cancer (SPCRC) refers to a new primary cancer in the colon or rectum diagnosed in a person with a previous diagnosis of colorectal cancer. A primary colorectal cancer can be diagnosed at the same time as the first primary colorectal cancer (FPCRC) in which case they are referred to as synchronous primary colorectal cancer, or at a later date, in which case they are referred to as second primary colorectal cancers (SPCRC) or metachronous colorectal cancers.[2]

Oestrogen has been found to regulate growth, differentiation and functioning of cells in the gastrointestinal tract in experimental studies.[3,4] Previous epidemiological studies suggested that use of hormone replacement therapy (HRT) associated with reduced risk of colon cancer among menopausal women,[5–8] while the observations on the association between hormone replacement therapy (HRT) and risk of rectal cancer are inconsistent.[9–12] Moreover, it is still unclear how change of female hormone level after menopause may influence the risk of metachronous colorectal cancer.

The effect of oestrogen may be influenced by the expression of oestrogen receptors of the target cells. The study by Konstantinopoulos and colleagues and the study by Foley

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doi:10.1016/j.ejca.2007.05.015

and colleagues indicated expression of oestrogen receptor beta (ERβ) was much lower in colon adenocarcinoma tissue than in normal colon tissue, and decreased parallel with the loss of differentiation of the colon tumours.[13,14]

In this study, the gender-age-specific incidence rates of second primary colorectal cancer (SPCRC) with different Grade, which indicates loss of differentiation, are calculated and compared. The interaction effects of age and sex on the risk of a second primary colorectal cancer (SPCRC) in different Grade are then further adjusted in multivariate Poisson regression models.

2. Materials and methods

2.1. Data source

This study is a retrospective cohort study using cancer registry data covering the period 1973–2003 obtained from the Surveillance, Epidemiology, and End Results (SEER) Programme of the National Cancer Institute (www.seer.cancer.gov). Individuals are identified within each registry by a unique identifier. This person identifier in combination with the registry identifier enables all cancers for an individual within a registry to be linked. In the SEER data, cancer site, cancer histology, and cancer behaviour were coded by ICD-O-2 (International Classification of Diseases for Oncology, 2nd Edition). This enabled both *in-situ* and malignant cancers at different anatomic sites to be identified. Tumour grade was classified as Grade 1 (well differentiated), Grade 2 (moderately differentiated), Grade 3 (poorly differentiated), Grade 4 (undifferentiated) and tumour grade not determined. For this study, all patients with first primary invasive colorectal cancer were identified and extracted (ICD-O-2; C180-C189, C260, C199, C209).

2.2. Statistical analysis

In primary descriptive analysis, it was observed that the annual incidence of second primary colorectal cancer decreased by about 50% in the first 5 years after the diagnosis of FPCRC, and became relatively constant after that. It is likely that a large proportion of cancer cases diagnosed in the first 5 years after the diagnosis of the first primaries have already existed at or before the time when the first primaries were diagnosed, and were picked up during the intensive surveillance following the surgical treatment of the first primaries. These cases should not be considered as incident metachronous cancer cases. Therefore the follow-up period of the first 5 years after diagnosis of the first primary colorectal cancer (FPCRC) was excluded from the analysis.

Moreover, all cancer diagnoses were excluded if they were death certificate notification cases, autopsy findings, without histological confirmation, or *in-situ* cases.

To calculate the age-specific incidence of SPCRC, person-years were categorised by age in 5-year groups, allowing the age-specific incidence to be determined.

The incidence of metachronous colorectal cancer was determined by dividing the total number of individuals with a second primary colorectal cancer (SPCRC) diagnosis by the total person-years of observation accumulated by all patients with a first primary colorectal cancer (FPCRC) at risk. Person-years at risk were calculated for each individual from 5 years after the diagnosis of their first invasive colorectal cancer until the date of diagnosis of a metachronous colorectal cancer, date of death, or 31 December 2003, whichever came first.

In the multivariate analysis, Poisson regression models were conducted separately to estimate the interaction effects of sex and age on the risk of second primary colon cancer and second primary rectal cancer, adjusting for race, period of follow-up, tumour stage and grade of the FPCRC, and calendar period for diagnosis of the FPCRC.

In the multivariate analysis, age was separated into <70 and $\geqslant$70. The caecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon (ICD-O-2 C180 to C189 and C260) were classified as colon, while rectosigmoid junction and rectum (ICD-O-2 Code C199, and C209) were classified as rectum. Race was categorised into White, Black and Other. The 6–31 years of follow-up was separated into five categories: 6–10 years, 11–15 years, 16–20 years 21–25 years and 25–31 years. The calendar period of diagnosis was categorised into three time periods 1973–1979, 1980–1989, and 1990–2003. Poisson distribution was assumed for the analysis.

Six pairs of crude and adjusted Poisson models were fitted separately for Grade 1, Grade 2, and Grade 3 second primary colon cancer and second primary rectal cancer.

In each adjusted model a variable representing the interaction term and main effects of age and sex was first tested, and then a new variable with four categories representing the matrix of age and sex was created, and put in the six pairs of crude and adjusted Poisson models instead to compare the risk among patients in different sex-age groups. The STATA. 9 software package was used for the analysis.

3. Results

A total number of 801,461 person-years were included in the analysis, and 2344 SPCRC cases were observed. About 55% of all SPCRC cases were classified as Grade 2— moderately differentiated. The overall incidence rates were significantly higher in males than in females for Grade 1 SPCRC, but were significantly higher in females than in males for Grade 3 SPCRC. The incidence rates were similar for both sexes in Grade 2 SPCRC. (Table 1).

The age-specific incidence rates of Grade 1, Grade 2 and Grade 3 SPCRC were calculated separately for the each 5-year strata in the age range of 45 to 94 (Fig. 1). The age-specific incidence rates were not calculated for Grade 4 SPCRC, because only 16 cases were observed, and for the same reason, the age-specific incidence rates before the age of 45 were not calculated (only 23 cases for that age range).

Overall, the age-specific incidence of Grade 1 SPCRC was always lower in females than in males, especially before the age of 65, whereas the age-specific incidence of Grade 2 SPCRC was higher in males than in females at ages under 65 years but relatively similar for ages 65 and older. In contrast, age-specific incidence of Grade 3 SPCRC appeared to be higher in females than males in older age groups with little difference in younger age groups. These were due to a larger increase in the incidence of Grade 2 and Grade 3 SPCRC in females than in males when progressing to higher age.

Table 1 – Incidence of Grade 1, Grade 2, Grade 3, and Grade 4 SPCRC in males and females 5 years after diagnosis of FPCRC

Sex	Number of total cases (colon cases, rectal cases)	Person-time at risk	Incidence rate (per 1000 person-years)	95% Confidence interval	
Grade 1 SPCRC					
Males	146 (112, 34)	377,067	0.39	0.33	0.46
Females	110 (97, 13)	424,394	0.26	0.22	0.31
Grade 2 SPCRC					
Males	610 (515, 95)	377,067	1.62	1.49	1.75
Females	682 (578, 104)	424,394	1.61	1.49	1.73
Grade 3 SPCRC					
Males	161 (128, 33)	377,067	0.43	0.37	0.50
Females	261 (235, 26)	424,394	0.61	0.54	0.69
Grade 4 SPCRC					
Males	9 (9, 0)	377,067	0.02	0.01	0.05
Females	7 (7, 0)	424,394	0.02	0.01	0.03
SPCRC with undetermined grade					
Males	183 (136, 47)	377,067	0.49	0.42	0.56
Females	175 (129, 46)	424,394	0.41	0.36	0.48

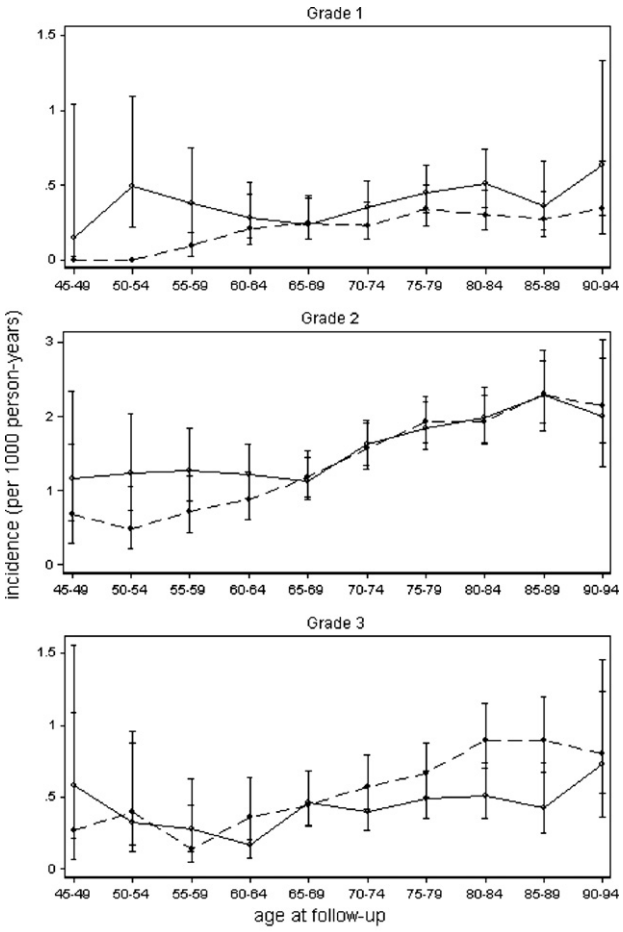

Fig. 1 – Age-specific incidence of grade-specific SPCRC by sex. The dots connected by the solid curve represent the age-specific incidence in males; the dots connected by the dash curve represent the age-specific incidence in females; the range spike represents the 95% confidence intervals.

It is also indicated in the figure that interaction effects between sex and age on the risk of Grade 2 and Grade 3 SPCRC may exist as the age-specific incidence curves for males and females cross at the age range of 65–69.

The incidence rates of second primary colon cancer and second primary rectal cancer by sex and age (<70 and 70+) were also calculated (Table 2). In males the incidence rate of second primary colon cancer in the younger age group was only about 30% lower than that in the older age group, but among females the incidence rate in the younger age group was 50% lower than the rate in the older age group. The incidence rate of second primary rectal cancer was relatively similar among males between the two age groups, and was also similar to that of females in the older age group. However, among females, the incidence rate in younger age group was still 36% lower than the rate in older age group.

The results from Poisson regression models on the interaction effects of sex and age are shown in Table 3. Overall, the crude incidence rate ratios appeared to be similar to the adjusted estimations. The risk of Grade 1 second primary colon cancer did not appear to be affected by age in both sexes, and the interaction effect of sex and age on the risk of Grade 1 second primary colon cancer was insignificant. The risk of Grade 2 second primary colon cancer was lower in females than in males when comparing the younger age groups, but the risk was similar between the two genders in the older age group, though the interaction effect of sex and age was also found to be insignificant. The interaction effect of sex and age was significant for the risk of Grade 3 second primary colon cancer. The risk of Grade 3 second primary colon cancer was similar between females and males in the younger age group, and the risk also appeared to be similar between the two age groups among males. However, among females the risk of Grade 3 second primary colon cancer in the older age group was about twice that in the younger age group.

The risk of Grade 1, Grade 2, and Grade 3 second primary rectal cancer appeared to be slightly higher in the

Table 2 – Incidence of second primary colon cancer and second primary rectal cancer by sex and age 5 years after diagnosis of FPCRC

Sex and age		Number of cases	Person-time at risk	Incidence rate (per 1000 person-years)	95% Confidence interval	
Second primary colon cancer						
Males	<70	260	136,641	1.90	1.69	2.15
	70+	640	240,427	2.66	2.46	2.88
Females	<70	186	130,717	1.42	1.23	1.64
	70+	860	293,678	2.93	2.74	3.13
Second primary rectal cancer						
Males	<70	68	136,641	0.50	0.39	0.63
	70+	141	240,427	0.59	0.50	0.69
Females	<70	42	130,717	0.32	0.24	0.43
	70+	147	293,678	0.50	0.43	0.59

Table 3 – Incidence rate ratio of interaction between sex and age for Grade 1, Grade 2 and Grade 3 second primary colon cancer and second primary rectal cancer

Matrix by sex and age		Crude incidence rate ratio	95% Confidence interval		Adjusted incidence rate ratio	95% Confidence interval	
Second primary colon cancer							
Grade 1[a]							
Males	<70	0.87	0.54	1.42	0.88	0.54	1.43
	70+(ref)	1.00			1.00		
Females	<70	0.61	0.35	1.08	0.62	0.35	1.09
	70+	0.72	0.48	1.08	0.70	0.46	1.04
Grade 2[a]							
Males	<70	0.62	0.49	0.79	0.63	0.50	0.80
	70+(ref)	1.00			1.00		
Females	<70	0.51	0.39	0.66	0.51	0.39	0.66
	70+	1.07	0.91	1.25	1.05	0.90	1.24
Grade 3[b]							
Males	<70	0.99	0.64	1.53	0.98	0.63	1.52
	70+(ref)	1.00			1.00		
Females	<70	0.91	0.58	1.44	0.90	0.57	1.43
	70+	1.99	1.46	2.71	1.91	1.40	2.60
Second primary rectal cancer							
Grade 1[a]							
Males	<70	0.97	0.41	2.28	0.82	0.35	1.96
	70+(ref)	1.00			1.00		
Females	<70	0.25	0.07	0.88	0.21	0.06	0.77
	70+	0.33	0.13	0.84	0.32	0.13	0.84
Grade 2[a]							
Males	<70	0.85	0.51	1.41	0.82	0.49	1.37
	70+(ref)	1.00			1.00		
Females	<70	0.61	0.34	1.10	0.58	0.32	1.03
	70+	1.06	0.72	1.55	1.03	0.70	1.51
Grade 3[a]							
Males	<70	0.57	0.23	1.43	0.53	0.21	1.33
	70+(ref)	1.00			1.00		
Females	<70	0.51	0.19	1.35	0.46	0.17	1.23
	70+	0.60	0.30	1.20	0.60	0.30	1.21

a Interaction effect between sex and age was insignificant in the adjusted model.

b Interaction effect between sex and age was significant in the adjusted model. Multivariate model adjusted for race, period of follow-up, calendar period of diagnosis of FPCRC, grade and histological stage of FPCRC.

older age group than in the younger age group for both sexes, and the risk difference by age was most obvious for Grade 2 second primary rectal cancer among females. No significant interaction effects of sex and age on the risk of grade-specific second primary rectal cancer were observed.

4. Discussion

The age-specific incidence rates comparison indicated that the risk of Grade 1, Grade 2 and Grade 3 SPCRC increased with age. This observation was further confirmed in the multivariate analysis. The increase of incidence across age was much

less aggressive than that of first primary colorectal cancer, which increases about ten times from the age of 45 to the age of 75.[15,16] The studies by Shureiqi and colleagues[17] and Levi and colleagues[18] reported that the incidence ratio of SPCRC to FPCRC was decreased sharply as age increased. Their findings could be explained as the background incidence of colorectal cancer (in the population) increases steeply with increasing age, whereas this rise is much less marked among colorectal cancer survivors.

The incidence rates of SPCRC appeared to increase much more rapidly in females than in males after the age of 55. These results may suggest that the change of female hormone level my influence the risk of SPCRC. Postmenopausal female hormone use was found to associate with a lower risk of colon cancer.[6,7] It is plausible that the sharp decrease of female hormone during the menopausal age may increase the risk of second primary colorectal cancer leading to an obvious increase of SPCRC risk among females after the age of 55–59. Nevertheless, a colorectal tumour may need about 10 years to develop from a polyp,[2,19] while studies suggest that oestrogen may reduce the risk of colorectal cancer by inhibiting the grow of small polyps.[20] This may explain why the incidence of Grade 2 and Grade 3 SPCRC in females reaches the incidence level in males about 15–20 years after females become postmenopausal.

The incidence of Grade 3 second primary colon cancer was even higher in females than in males after the age of 75, whereas the curve of Grade 1 SPCRC for males and females was mainly parallel. In the multivariate analysis, the interaction effect of sex and age on the risk of Grade 3 second primary colon cancer was also found to be significant. Again this agreed with previous experimental studies looking at association between oestrogen and colon cancer. It was found that the expression of oestrogen receptor beta (ERβ) was much lower in colon adenocarcinoma tissue than in normal colon tissue, and decreased parallel to the loss of differentiation of the colon tumours.[13,14] Oestrogen has been found to regulate growth, differentiation and functioning of cells in the gastrointestinal tract in experimental studies.[3,4] The observations of this study may indicate that a sharp decrease of female hormone level increases the risk of a second primary colon cancer, especially a cancer with poorer differentiation.

It was also found that the incidence rate of second primary rectal cancer was considerably higher in the older age group among females, but among males the incidence was similar between the two age groups (Table 2). Nevertheless, the interaction effect of sex and age was not significant for Grade 1, Grade 2 or Grade 3 second primary rectal cancer. This might be due to the fact that only a small number of second primary rectal cancer cases were observed among females in the younger age group. However, it may also be possible that a decrease in plasma female hormone level has a much weaker effect on the risk of second primary rectal cancer, as it has been observed in some previous studies that use of hormone replacement therapy among menopausal women only reduces the risk of colon cancer but not of rectal cancer.[8,10,11]

4.1. *Limitation*

This study is using SEER cancer registry data covering the period 1973–2003. Classification for differentiation of colorectal tumour may vary over time, but the effect of calendar period had been adjusted in all of the multivariate Poisson models, and the interaction between sex and age was significant for Grade 3 second primary colon cancer. Moreover, no strong confounding effect was detected in the Poisson models, as all significant crude incidence rate ratios changed less than 5% after adjusting for confounding effects.

The interaction effects of sex and age observed varied for second primary colon cancers with different levels of differentiation; this observation is very unlikely to be introduced by confounders. Some women may also undergo HRT after menopause, and this may weaken the interaction effects of sex and age.

5. Conclusion

This study showed that the risk of Grade 1, Grade 2, and Grade 3 SPCRC increased gradually with age, especially for Grade 2 and Grade 3 SPCRC. Females had lower risk of SPCRC in any Grade than males before the age of menopause, but higher risk of developing higher Grade SPCRC than males after the age of 70. It was also observed that there was significant interaction effect between sex and age on the risk of Grade 3 second primary colon cancer. No such significant interaction effect was found on the risk of Grade 1 and Grade 2 second primary colon cancer, or on the risk of second primary rectal cancer. Combining evidence from previous experimental studies, it is likely that decrease in female hormone level after menopause increases the risk of a second primary colon cancer, especially a cancer with poorer differentiation.

Conflict of interest statement

None declared.

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