and other possible sources of error or bias may, at first sight, appear mere speculations. However, after the amount of epidemiological research which has systematically tended to reproduce, with remarkable consistency, an association between coffee and bladder cancer, even apparently less plausible hypotheses should be considered, and, if possible, tested in future research.

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Acknowledgements—This work was conducted within the framework of the National Research Council (CNR), Applied Projects "Oncology" (Contract No. 87.01544.44) and "Prevention and Control of Disease Factors" (Contract 91.00285.PF41), and with the contribution of the Italian Association for Cancer Research and the Italian League Against Tumours, Milan. B.D. was a recipient of the Nella Bangera fellowship. We thank Ms. J. Baggott, Ms. Ivana Garimoldi, and the "G.A. Pfeiffer" Memorial Library staff for editorial assistance.

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1484–1487, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

The Effect of Family History of Cancer, Religion, Parity and Migrant Status on Survival in Colorectal Cancer

Data from the Melbourne Colorectal Cancer Study

Gabriel A. Kune, Susan Kune and Lyndsey F. Watson

The association between 5-year survival and several risk factors was investigated in 705 histologically confirmed, new cases of colorectal adenocarcinoma as one aspect of a comprehensive population-based study of large bowel cancer incidence, aetiology and survival—the Melbourne Colorectal Cancer Study. 5-year survival was not influenced by the previously determined risk of a family history of colorectal cancer in near-relatives. Similarly, other previously determined risk factors of religion, number of children, age at birth of first child and migrant status did not influence survival.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1484–1487, 1992.

INTRODUCTION

COLORECTAL CANCER remains one of the commonest cancers in the world and is particularly common in developed societies. An understanding of the factors which determine survival in this cancer is particularly relevant to enable accurate prognostication in an individual case and also in the study of the natural history of colorectal cancer.

This communication is based on data derived from the Melbourne Colorectal Cancer Study which is a large, comprehensive, epidemiological and clinicopathological investigation of large bowel cancer incidence, aetiology and survival [1, 2]. This study has three main arms, the incidence study, the case-control study and the survival study. The incidence study determined the demographic variables, the case-control study examined all the hypothesised aetiological and risk factors such as diet and heredity, and the survival study examined survival in this group of patients.

The data for this paper are derived from both the case control and the survival arms of the study. The aim of this communication was to examine whether certain factors which are known risks for this cancer, such as a family history of

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Revised and accepted 7 Jan. 1992.

colorectal cancer, have an influence on survival, independently of the traditional survival determinants, such as the stage of the cancer. The traditionally considered determinants of survival, namely age, sex, cancer stage, cancer site, cancer cell differentiation and bowel perforation have already been described in detail in another communication [3].

SUBJECTS AND METHODS

Cases included

The study was conducted in Melbourne, Australia, and specifically the Melbourne Statistical Division (MSD) which included the whole of urban Melbourne, and had a population of 2.81 million at the time of the study. The cases included all histologically confirmed new cases of colorectal adenocarcinoma diagnosed during the 12 month period 21 April 1980–20 April 1981 and who were usual residents of the MSD. There were 1140 cases in the incidence study, of which 715 (63%) were included in the case control arm of the study. In 10 of the 715 cases, accurate data on staging was not available, leaving 705 cases who had all the required information for this part of the study. As described subsequently, the age, sex and stage distribution of the 705 cases analysed here was very similar to that of the 1140 cases in the incidence study, indicating that the 705 cases are highly representative of the total group.

Factors examined

Traditional survival determinants. To verify the representativeness of the sample, the accepted determinants of survival, and in particular cancer stage, were examined. For cancer stage, Dukes classification was used for Stages A, B and C as initially defined by Dukes for rectal cancer [4, 5] and subsequently also widely used for staging colon cancer; A (cancer limited to bowel wall), B (cancer spread by direct continuity outside bowel wall but not invading the lymph nodes) and C (metastases present in the regional lymph nodes). Stage D was added to Dukes classification by the present authors to include all advanced, so-called "incurable" cases, that is, cases with distant metastases, peritoneal seedlings, extensive local involvement in which malignant tissue was known to have remained after resection, and when there was extensive extra bowel involvement and no resection was performed [3]. Also examined were age, sex, cancer site (colon or rectum), type of cancer (first and single, synchronous or metachronous cancer), degree of cell differentiation, and the presence of perforation, as factors of interest with respect to survival [3].

Risk factors examined. The aspects investigated were those which were unlikely to change with the diagnosis and treatment of the colorectal cancer. The factors examined in relation to survival in this part of the study included migrant status (as measured by country of birth), religion, family history of colorectal cancer, number of children and age at birth of first child. A family history of colorectal cancer in close relatives was found to be a risk [6], and having no children or having children late in life were also found to be risks for colorectal cancer [7]. Those of the Jewish religion were also found to be at risk [8]. The risk levels of various migrant groups in Australia were also previously examined in this study [8] and were included as a factor in this survival analysis.

The previously identified dietary risk factors [9] were not included, because dietary data were not available post diagnosis and treatment and meaningful conclusions regarding survival in relation to presymptom diet would not have been reasonable. Regrettably, no information was available on perioperative blood transfusion, as the study was performed before the issue of survival in colorectal cancer in relation to perioperative blood transfusion had been raised.

Statistical analysis

The data file handling and manipulation, cross tabulation and life table estimation of survival rates were carried out using SPSSx [10]. The assessment of the effect of covariates on survival was made using Cox's proportional hazards regression modelling in BMPD [11, 12]. The analysis proceeded according to the following steps: (1) comparison was made in survival rates between those in the case-control study and those unable to be satisfactorily interviewed and therefore weighted out in the analysis for this paper, but included elsewhere [3]. (2) Life tables for colon and rectal cancer separately were produced by sex and stage and for both observed and relative survival rates. Observed survival rates are based on death from all causes, whereas relative (or adjusted) survival rates use deaths from colorectal cancer only and treat death from other causes as a censored survival time. (3) As described below in the section dealing with the results, there was a markedly different survival pattern for stage D compared with the other three stages. Because of this difference, two assumptions were made. The first assumption was that the covariates of interest would have the same effect for each of stages A, B and C, and could be analysed together. The second assumption was that stage D represented such a heterogeneous extent of disease that the results of any survival analysis of the covariates of interest would not be meaningful and was not proceeded with. Therefore, a regression model was fitted for stages A, B and C together, and in each of these, the co-variates were fitted one by one and then in combinations until models containing variables of significant effects were obtained.

RESULTS

Of the original 1140 cases, there were 35 who did not have adequate pathological staging of their cancer. Analysis of the 1105 incident cases using Cox's proportional hazard regression modelling with covariates of sex, age, site (colon, rectum), tumour type (single, metachronous, synchronous), bowel perforation, degree of cell differentiation and also interview status (that is, whether interviewed or not), showed that interview status was highly associated with survival. Death rate for those not interviewed was twice as high as for those interviewed ($P < 0.001$). This is quantifying the evident fact that there exists a significant selection bias with respect to survival, namely that early deaths are less likely to be interviewed. The analysis of the 705 cases that follows should therefore be considered as a conditional one, conditional on peridiagnosis survival.

The average age of the 705 in this analysis was 66 years (SD 11) and this also applied to the total sample of 1105 cases. The minimum age was 20 and the maximum age was 93 years. There were 390 colon cancers (201 males, 189 females) and 315 rectal cancers (181 males, 134 females). There were thus a total of 382 or 54% males (51% males in the total sample of 1105) and 323 (or 46%) females (49% in the total sample of 1105). There were 16% in stage A (15% stage A in total sample of 1105), 32% in stage B (32% stage B in total sample), 28% in stage C (25% stage C in total sample) and 24% in stage D (29% in total sample). Of the 536 classified stage A, B or C, 10 (2%) had bowel perforation and for 29 (5%) this data was not available, while for stage D, 10 (6%) had bowel perforation and for 30 (18%) this data

Table 1. 5-year survival rates and median survival time by Dukes stage and site

	No.	Observed survival rate	Median survival time (months)	Adjusted survival rate	Median survival time (months)	S.E. of adjusted survival rate
Dukes A						
Colon	45	0.84	84+	0.88	84+	0.05
Rectum	68	0.74	84+	0.84	84+	0.05
Dukes B						
Colon	140	0.65	84+	0.76	84+	0.04
Rectum	89	0.52	63	0.60	84+	0.06
Dukes C						
Colon	114	0.44	40	0.48	49	0.05
Rectum	80	0.36	36	0.39	40	0.6
Dukes D						
Colon	91	0.09	12	0.11	12	0.03
Rectum	78	0.00	11	0.00	11	

was unavailable. For stages A, B and C, 13% had poor cell differentiation, 61% had moderate cell differentiation, 20% had good differentiation and in 6% cell differentiation was not known. In stage D, the percentages for cell differentiation were 19% poor, 59% moderate, 12% good and in 10% cell differentiation was not known.

The 5-year survival and median survival for the several stages is shown in Table 1. As expected, this indicates a decreasing survival with more advanced stages for both sites and both sexes. When the hazard rates were plotted for each stage, these were similar and approximately parallel for stages A, B and C, whereas the hazard for stage D was markedly different, indicating a heterogeneous group of cases and further analysis of stage D was not proceeded with.

The effect of the covariates was then examined using the Cox proportional hazards regression method for stages A, B and C together. For stages A, B and C combined, the factors which statistically significantly affected survival were age, site, and cell differentiation. With increasing age, survival was worse. Survival was worse for rectal cancer than for colon cancer. The poorer the cell differentiation, the poorer the survival. Religion was not associated with survival. None of the other factors, namely sex, migrant status, family history of colorectal cancer, number of children and age at birth of the first child, were statistically significantly associated with survival in the combined analysis of Dukes stages A, B and C (Table 2).

Table 2. Cox proportional hazard regression model for survival in colorectal cancer. Measure of the effect of covariates

	Stages A, B and C		
Covariate	Exponential of regression coefficient	95% CI	*P* value
Age	1.013	1.00–1.03	0.05
Sex	0.876	0.66–1.16	0.36
Site	1.443	1.09–1.91	0.01
*Covariate			
Cell differentiation	0.723	0.56–0.93	0.01
Tumour type (single vs other)	0.996	0.86–1.15	0.99
Perforation	1.342	0.76–2.38	0.32
Family history of colorectal cancer	1.125	0.77–1.65	0.54
No. of children	1.009	0.85–1.20	0.92
Age at birth of first child	0.991	0.96–1.02	0.54
Migrant status	1.065	0.78–1.46	0.70

*Adjusted for age, sex and site.

DISCUSSION

The traditionally known factors in survival are important for colorectal cancer. In particular, the stage of the cancer, was again shown to be the most important single discriminant of survival. The stage of the cancer has been discussed previously [3, 13–16]. However, because of the importance of staging in survival, in the analysis of all other factors considered, the cases must be stratified by stage. Similarly, other traditional pathological factors such as the site of the cancer, the type of cancer, i.e. whether it is the first cancer, a synchronous or a metachronous cancer, the degree of cell differentiation and the presence or absence of bowel perforation have been fully discussed in another communication [3], and here are inserted into the proportional hazards equation because they have been found to be significant survival factors. The main thrust of the present discussion will be on a considering the role of the risk factors in survival which are considered in this part of the study over and above staging and other previously described and known pathological factors.

In the Melbourne study, a positive family history of colorectal cancer was associated with a 2–3-fold risk [6] and similar estimates of risk have also been found in other previous studies [17–19]. It was, therefore, of interest in this analysis that a positive family history of colorectal cancer had no effect on survival, that is, survival was neither better nor worse in the presence of a positive family history of colorectal cancer when compared with those who did not have this family history. This is an important finding, which has not been previously investigated. In the Melbourne study, a positive family history of colorectal cancer was independent of other risk factors and was therefore regarded as a reasonably good index of a genetic predisposition to this cancer [6]. This finding cannot be compared with other data, as the literature is silent on the relationship between survival in colorectal cancer and a family history of this cancer.

Religion had no influence on survival in any of the stages of colorectal cancer. This was of interest, because in the incidence arm of the study, it was found that Jews had a 2-fold risk for colorectal cancer when compared with members of other religions [8] and similar risk levels were noted for Jews in previous studies [20–21].

In the Melbourne study, it was found that having children and having the first child at an early age was protective for colorectal cancer in both males and females [7] and similar findings were reported for both males and females in a recent cohort study [22]. It was, therefore, of interest that the number of children and age at first birth had no effect on survival.

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Acknowledgements—This work was supported by grants from The Nicholas and Elizabeth Slezak Cancer Research Fund of the University of Melbourne.

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1487–1490, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Linkage of Death Certification of AIDS and Cancer Registration in Vaud, Switzerland

Silvia Franceschi, Fabio Levi, Isabelle Rolland-Portal and Carlo La Vecchia

58 death certifications (40 males and 18 females) of residents of the Canton of Vaud (Switzerland) which reported AIDS as the cause of death in 1986–1989 were matched with the list of incident cancers available since 1974 from the Vaud Cancer Registry. Such linkage was successful for 20 individuals (age range 25–63, median 37), mostly males (18/20), homosexual or bisexual (11/18) and affected by Kaposi's sarcoma (14 males and 1 female). Other identified neoplasms included one Burkitt's lymphoma, one prostate adenocarcinoma and one multiple myeloma (whose histological picture included, however, lymphocytosis in addition to plasmocytosis). Three additional malignancies (one undifferentiated skin cancer, one carcinoma of the salivary glands and one *in situ* cervical carcinoma), and one myelodysplastic syndrome had also been diagnosed from 1 to 2 years before AIDS death. Cancer was mentioned on the death certificate, in addition to AIDS, in only 2 cases. Albeit of limited size, the present report confirms that a systematic integration of AIDS and cancer registration statistics provides additional information, of particular interest for histological classification, on the AIDS–cancer relationship.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1487–1490, 1992.

INTRODUCTION

SINCE THE onset of AIDS epidemic the relation between AIDS and cancer has been clear, both from a research point of view (following accrual of knowledge on viral carcinogenesis, growth factors, new drugs and biotechnological advances, whose benefits are likely to be shared by AIDS and cancer research as well) and in clinical terms (since certain neoplasms complicate the course of many patients with AIDS) [1].

With the predictable increasing size of the population affected by AIDS and of individuals immunosuppressed on account of preclinical infection from human immuno-deficiency virus (HIV), it is easy to predict that AIDS is going to have an important impact on cancer statistics, particularly in young and middle-aged adults. Such impact is likely to be both quantitative, hence leading to the proportional increase of incidence and mortality rates from a few formerly rare neoplasms, and qualitative. Indeed, cancers which are known (i.e. Kaposi's sarcoma, and non-Hodgkin's lymphoma) or suspected (e.g. Hodgkin's disease, cancer of the oral cavity, liver, anus and cervix uteri) to be related with AIDS have been shown to manifest themselves, not only more frequently, but also differently in AIDS patients than in the general population [2–4]. Unprecedented degrees of complication in the histological characteristics, clinical evolution and, most of all, frequency of synchronous and metachronous