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The Incidence of Colon, Breast and Prostate Cancer in Italian Migrants to Victoria, Australia

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The incidence of cancers of the colon, breast and prostate in Australian and Italian born residents of Victoria, Australia were compared with the incidence of these cancers in Italy. Italian migrants' rates were between those of the Australian born and those from Italian cancer registries. Italian migrants' rates for colon cancer (males 23.1 and females 15.8 per 100 000) differed from rates in Ragusa (males 12.1 and females 10.4 per 100 000) but not from rates in Parma or Varese. The migrants' breast cancer rate was similar to the rate in Ragusans (48.7 vs 46.7) and their prostate cancer rate of 27.3 was higher than all Italian registries. Modelling identified that Italian migrants' rates by age were intermediate to Australian and Italian rates, but indistinguishable from cancer rates in Ragusa, except for colon cancer which demonstrated an interaction with age.
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INTRODUCTION

Epidemiologists have used international differences in cancer rates and changes in cancer rates in migrant populations to infer an environmental component in the aetiology of various forms of cancer [1]. Typically, migrants from low risk countries to high risk countries have demonstrated lower cancer rates than the population of the new host country and vice versa. Classic studies [2] include those of migrants to the U.S.A. where, for example, the first generation have higher rates of colon cancer than in the homeland countries and the second generation have higher rates than their parents—rates that approach those of the U.S.A. population. Migrant populations in Australia have also contributed to this debate. In addition to confirming trends shown in other populations, information on duration of residence which is routinely collected on death certificates and at the census, permits some stratification of cancer mortality rates by length of exposure to the Australian lifestyle. To date, similar analyses have not been conducted for cancer incidence. These data have recently been reviewed [3]. One of the largest migrant populations is from southern Europe—a region of contrasting cancer patterns to Australia. Apart from lung cancer, the most frequently occurring cancers in Australia are bowel, breast and prostate. Mortality from each of these cancers is lower in southern European migrants but with increasing residence these differences diminish.

Much emphasis has been placed on the role of diet and other lifestyle factors in the aetiology of cancers of the bowel, breast and prostate and migrant data have been used to support this. The increases in risk after middle age for bowel cancer in migrants from low risk countries of origin have been interpreted as a possible late stage promotional effect of dietary change [4]. However, this may not be the only explanation. It is possible that migrants are selected for their good health and may differ in important respects from the natives of their new country or the non-migrants remaining in the countries of origin. Apart from this "healthy migrant" or selection effect, genetic differences in susceptibility also have to be considered. It is also possible that significant environmental exposures took place in early life prior to migration, and that these have had a lengthy protective effect.

One argument for an environmental basis to the differences in incidence of cancers of the colon, breast and prostate has been the increase in mortality in cancers with increasing duration of residence in Australia. This phenomenon, however, could be explained by the migrant's cancer incidence being linked to their native cohort's risk. The early deficit of cancer compared to Australians could be due to a healthy migrant effect; and the increasing incidence with increasing duration of residence could be related to ageing of the migrant cohort producing cancers at a similar rate to the non-migrant cohort remaining in Italy. Although Italian migrants' cancer rates are considered to be in transition from low to high, it is likely that cancer rates in Italy have also increased in parallel with technological developments, standard of living, and death control. Notwithstanding these caveats, in the early 1980s the life expectancy of southern European migrants was 4–5 years longer, on average, than Australians [5].

Although there was some emigration from Italy to Australia prior to World War II, significant waves of migration rapidly increased during the 1950s and had tapered off by the early 1970s [6]. At the 1986 census there were 109 198 people of Italian birth residing in Victoria, the majority of whom had resided there for more than 30 years [7]. To pursue evidence for an environmental effect, it was decided to investigate the incidence of cancer in the Italian migrants resident in Victoria and to examine any effect of age and country of birth, by comparison with the cancer experience of Italian and Australian populations.

MATERIALS AND METHODS

Cancer incidence data were made available from the Victorian Cancer Registry (VCR) for the period 1982–1987 by age, sex and country of birth for cancers of the breast, colon and prostate. The VCR is a population-based registry with compulsory cancer reporting since 1982. Ascertainment is considered to be complete [8]. Denominator data were obtained from the 1981 and 1986 censuses and person years for non-census years were calculated by linear interpolation. Comparative incidence data were

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obtained from Cancer Incidence in Five Continents [9] for the Italian cancer registries of Ragusa (1981–1982), Parma (1978–1982) and Varese (1978–1981). All registries selected for comparison had similar levels of histological verification, proportions of cases identified from death certificates only, and mortality/incidence ratios to those described for Victoria [9]. Ragusa was selected for detailed comparison as the majority of Italian migrants to Australia this century have come from southern and insular Italy [10]. Further comparisons were made with incidence estimates published by Jensen *et al.* for the whole of Italy [11].

Age and sex specific incidence rates for breast, colon and prostate cancer were calculated for Australian and Italian born persons in the Victorian population. These were based on the average incidence for each of the three sites during 1982–1987. The corresponding age standardised rates were calculated using the World Standard population [12] to allow direct comparison between Victorian rates and those published in Cancer Incidence in Five Continents [9]. Confidence intervals (95%) were calculated for each rate as ± two standard errors of the rate. Standard errors were calculated using the method described by Holman *et al.* [13].

Recent methodological advances in the analysis of migrant data [14] were considered for the analysis of our data. As we possessed relevant population denominators, we decided to use Poisson regression. Modelling of the relative risk of each cancer by migrant status adjusting for age and sex, was carried out on Australian and Italian born Victorian and Ragusan data. The observed number of cases in each cell was regarded as an independent Poisson variable with mean value

$$E(X_z) = py_z \times \lambda_z,$$

where py_z is the person years of observation and λ_z the incidence rate in cell **z**. Thus,

$$\log E(X_z) = \log(py_z) + \beta'\mathbf{z}$$

where $\beta'\mathbf{z} = \log(\lambda_z)$. In this model, **z** is a matrix of explanatory variables, such as age, sex and country, pertaining to a given cell, while β' is a vector of regression coefficients for the explanatory variables. The model was fitted in GLIM [15], using the natural logarithm of the person years as the OFFSET team. The estimated regression coefficients were then used to obtain an estimate of the risk of cancer relative to the Australian born.

RESULTS

Age standardised rates

Comparisons of the age standardised rates for the Australian born, Italian migrants, the Italian cancer registries of Parma, Varese and Ragusa, and estimates for all of Italy are made in the form of graphs in Fig. 1. The graphs portray 95% confidence intervals for each rate estimate. The rates for Ragusa and migrants to Australia are based on smaller numbers than the other rates and are thus less precise. This is reflected in the increased width of the confidence intervals. The colon cancer incidence rate for males for the Australian-born (32.4) was significantly higher than other groups rates (Fig. 1a). The rates for Italian migrants (23.1), Parma (18.8) and Varese (20.8) were all significantly higher than the Ragusa rate (12.1) and the estimate for the whole of Italy (16.0). In females, the colon cancer rate was again significantly higher in the Australian-born (27.8) (Fig. 1b). The Italian migrant rate (15.8) did not differ

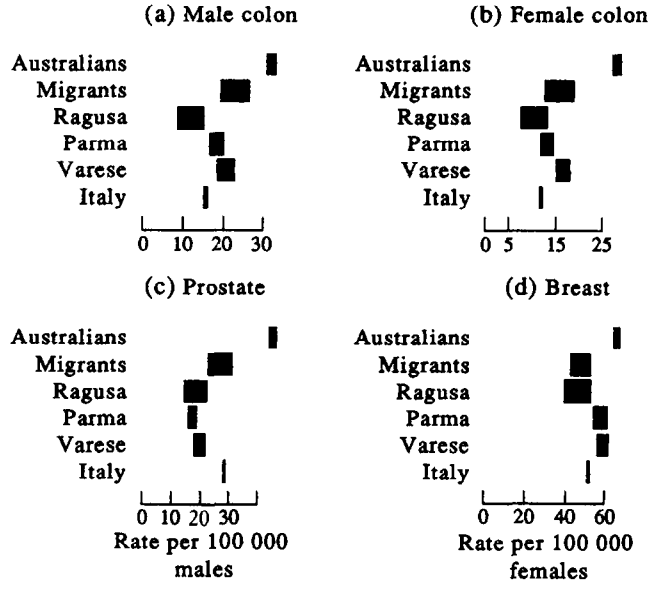

Fig. 1. The 95% confidence bands for the age-standardised rates of cancers of the colon, breast and prostate in the Australian-born and Italian-born in Victoria, Australia and in Italians from three Italian cancer registries and all of Italy.

from any of the Italian registry rates but was significantly higher than the estimate for the whole of Italy (11.9). The prostate cancer rate (Fig. 1c) for the Australian-born (45.5) was also significantly higher than all other groups. The rate for Italian migrants (27.3) was significantly higher than the rates reported by the Italian registries. The estimate for the whole of Italy (28.8) was also significantly higher than any of the Italian registry rates and was comparable to the Italian migrant rate (27.3). Female breast cancer (Fig. 1d) follows a somewhat similar pattern with the Australian-born having a significantly higher rate (67.0) than any other group, however, Parma and Varese both had significantly higher breast cancer rates (58.4 and 59.6, respectively) than Italian migrants (48.7), Ragusa (46.7) or the estimate for the whole of Italy (52.6).

Since most Italian migrants in recent decades have come from southern Italy, the principal comparison is to be made between the rates from Ragusa, the only cancer registry in the south of Italy, and the rates from the VCR. Overall, for males, the age standardised incidence rates for the Australian-born, Italian migrants and Ragusa were all significantly different from each other and were in the order expected with the migrants lying between the Australian and Ragusa rates. In females, the Italian migrant rates fell between the Australian and Ragusa rates but the rates for the two Italian groups were not significantly different from each other.

Poisson regression modelling of risk

The person years of observation by country of birth and sex are given in Table 1 with the number of observed cases of cancer. Results of the regression model are presented in Table 2. Both male and female Italians (whether migrants or from Ragusa) had significantly lower risks of developing cancer than Australian-born persons for any of the sites studied. As was expected for these cancers, the relationship between age and incidence rate was curvilinear. Interactions between age with migrant status and age with sex were present for colon cancer in the Italian migrants. Younger Italian migrants had a lower risk of colon cancer than their Australian-born counterparts while the older

Table 1. Person-years and incident case totals by site and country

Females	Person-years	Colon cancers	Breast cancers
Australian-born	4 885 555	3121	6527
Italian migrants	290 196	89	329
Ragusa	170 690	44	168
Males	**Person-years**	**Colon cancers**	**Prostate cancers**
Australian-born	4 438 903	2850	4147
Italian migrants	331 567	151	156
Ragusa	156 290	46	77

migrants had a risk comparable with older Australians. Across all groups, females had a higher risk of colon cancer than males at younger ages, but a lower risk at older ages. Prostate cancer risk was similar for the two Italian groups and both of these had significantly lower risks than Australian born males. There was no interaction between age and migrant status with respect to prostate cancer risk. Australian born women had a higher risk of developing breast cancer than either Italian migrants or women in Ragusa. The two Italian groups did not differ significantly in their risk and there was no interaction between age and migrant status. Goodness-of-fit, tested with Pearson's χ^2, was good for all final models.

Table 2. Results of Poisson regression modelling of risk relative to the Australian born

Parameter	Estimate	SE (estimate)	Δ deviance	df
Colon				
Age				
Linear component	2.013	0.066	8911.0	1
Quadratic component	−0.144	0.008	428.3	1
Migrant status				
Italian migrants	−1.329	0.285	170.0	2
Ragusan	−1.610	0.508		
Sex				
Female	0.243	0.107	49.1	1
Interactions				
Age × sex	−0.092	0.022	16.9	1
Age × Italian migrants	0.194	0.061	12.8	2
Age × Ragusa	0.131	0.103		
Prostate*				
Age				
Linear component				
Quadratic component	4.628	0.207	1	
	−0.349	0.021	1	
Migrant status				
Italian migrants	−0.533	0.082	124.0	1
Ragusans	−0.877	0.115		
Breast*				
Age			3277.0	1
Linear component	0 1.464	0.076	687.2	1
Quadratic component	−0.143	0.043		
Migrant status				
Italian migrants	−0.204	0.006	41.14	2
Ragusans	−0.395	0.078		

*Interaction terms were not significant.

Figure 2 shows the fitted age-specific rates for cancers of the male and female colon, prostate and female breast in the Australian born and Italian born residents of Victoria and those for Ragusa. In the case of breast and prostate cancers it is apparent that the incidence density curves are scalar shifts of each other indicating that incidence in all groups follows the same slope with increasing age but starts earlier and stays higher in Australians. The Italian migrants' incidence manifests a little later and the Ragusan incidence later still. For colon cancer, the curves for the Australians and Ragusans are virtually parallel while those for the migrants start close to the Ragusans at early age and end closer to the Australians in old age. This illustrates the interaction with age and migrant status in the model.

Dietary intake

Per caput intakes of selected dietary components were obtained from estimates made by the Food and Agriculture Organisation [16]. The average daily intakes per capita of certain nutrients for three separate triennial periods (1961–1963, 1975–1977, 1983–1985) are shown for Australia and Italy in Table 3. Australians obtained comparatively more of their nutritional intake of energy, fat and protein from animal products. A decrease in the average consumption of animal products between 1961–1962 and 1983–1985 was observed in Australia accompanied by an increase in vegetable consumption. In Italy, on the other hand, the consumption of animal protein and fat increased over this period as did the intake of beta carotene and ascorbic acid from both animal and vegetable sources. The ratios of Italian to Australian consumption of energy, fat and protein, all moved towards unity over time suggesting that the Italian and Australian diets were becoming similar in the quantity of animal and vegetable products consumed. Italians had consistently higher beta-carotene and ascorbic acid intakes than Australians.

DISCUSSION

The pattern of age-standardised rates in Australian migrants and Italians confirms previously observed differences [3–5]. The rates of breast, colon and prostate cancer being highest in Australian natives, lower in Italian registries (particularly Ragusa) and intermediate in Italian migrants. Given that the majority of Italian migrants to Australia are from southern and insular Italy, these differences are in the expected direction. Differences between cancer rates in Italian migrants and cancer rates from northern Italian registries are not so clear cut and are inconsistent across cancer types. Indeed, the northern Italian registries' incidence rates for breast cancer are intermediate to rates in Italian migrants and those born in Australia. The other data available for comparison are estimates made for the member states of the European Community. These tend to be within the range of confidence intervals for the Italian registry cancer rates except for prostate cancer where the estimate is higher than expected (see Fig. 1). Generally, the age-standardised rates are consistent with hypotheses of late stage changes in the incidence of these cancers in Italian migrants to Australia.

Poisson regression modelling failed to detect an interaction of age and country of birth between Australian born, Italian migrants and Ragusans for either cancer of the breast or prostate. The fitted incidence density curves with age for Italian migrants fall between those for Australians and Ragusans. The differences

Table 3. Intake of certain nutrients in Australia and Italy

		1961–1963	Ratio	1975–1977	Ratio	1983–1985	Ratio
Energy calories							
Vegetable	Aust	1813	1.38	2010	1.33	2225	1.14
	Italy	2493		2665		2526	
Animal	Aust	1329	0.37	1280	0.62	1118	0.86
	Italy	491		794		960	
Fat							
Vegetable	Aust	20.2	2.39	27.0	2.31	54.1	1.24
	Italy	48.3		62.3		67.2	
Animal	Aust	104.9	0.35	97.0	0.64	83.1	0.88
	Italy	36.8		61.9		73.2	
Protein							
Vegetable	Aust	32.4	1.66	32.7	1.62	35.1	1.40
	Italy	53.8		53.1		49.1	
Animal	Aust	63.4	0.47	70.6	0.64	61.3	0.91
	Italy	29.5		45.2		55.6	
β-carotene (equiv μg)							
Vegetable	Aust	2407	1.29	1983	1.94	3051	1.44
	Italy	3114		3851		4400	
Ascorbic acid							
Vegetable	Aust	76	1.74	84	1.89	100	1.75
	Italy	132		159		175	

between the groups for cancer of breast and prostate cannot be explained by an age/cohort effect. The migrants obviously have higher rates than Ragusans but are within the range of incidence estimates for all Italians. Is their apparent increase because of their transition from an Italian to an Australian culture and diet, or is it within the range of expected incidence in the cohort remaining in Italy?

Age period cohort analyses [17] of Italian mortality between 1955 and 1979 have demonstrated continuing increases (including recent cohorts) for colon (intestinal) cancer, whereas mortality from cancer of the breast has shown increases up to generations born in 1920–1930 and has stabilised thereafter. Prostate cancer mortality in Italy, has been stable for the generations born since 1900. Large regional differences have also been reported in Italian cancer mortality [18]. Mezzanotte *et al.* analysed data for northern, central and southern Italy and described a 2-fold difference between northern and southern Italy in age-adjusted mortality from intestinal cancers (30.1 vs. 13.5 in males, and 27.7 vs. 14.7 in females). Rates of breast and prostate cancer were also elevated in the north compared with the south (32.2 vs. 21.5 for breast, and 18.3 vs. 11.1 for prostate). In all instances, rates in the central region were intermediate to those in the north and south. These regional differences reflect the relative affluence and European culture of the north in comparison to the Mediterranean culture of the south, and are similar to the differences in cancer incidence seen between Ragusa and other Italian registries.

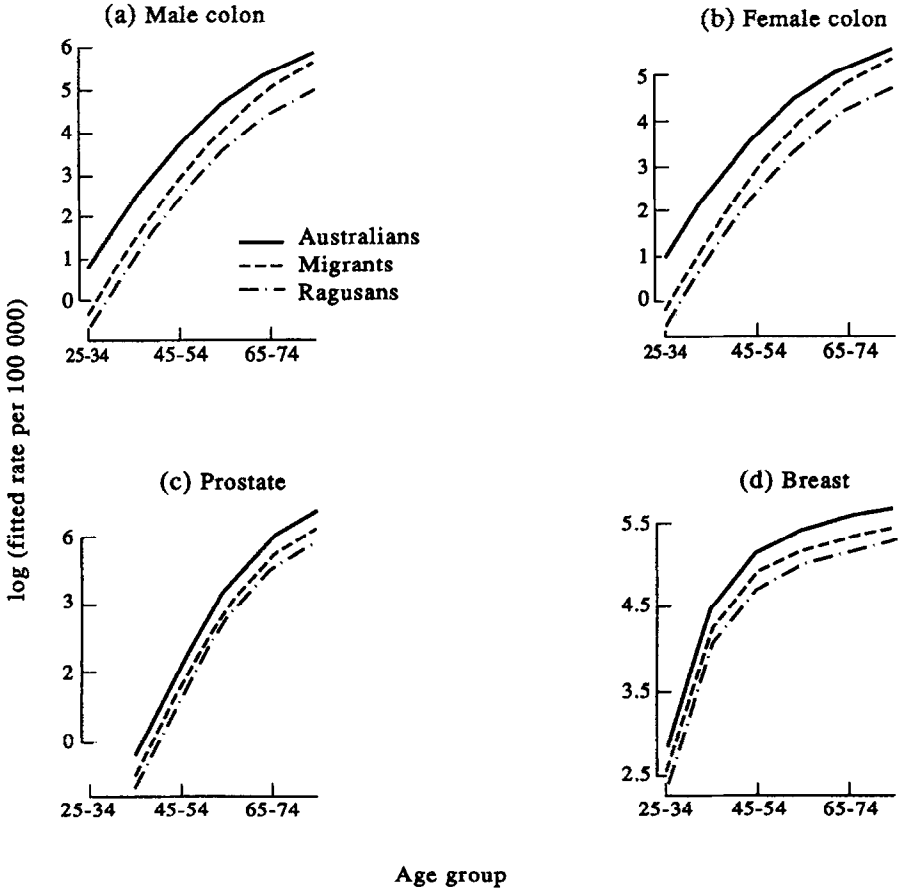

Fig. 2. The fitted age incidence density curves for cancers of the colon, breast and prostate in the Australian-born and Italian-born in Victoria, Australia and in Italians from the Ragusa Cancer Registry.

Prostate cancer mortality in Italian migrants is obviously converging with that in the Australian born but the effect is not as strong as that observed for colon cancer. The convergence of breast cancer mortality is even weaker. An explanation for these differences in convergence between the three cancer types might include the following considerations. First, early life events and exposures might be more important to the aetiology of breast and prostate cancer than exposures in later life. Second, cancers of the breast and prostate are hormone dependent, and dietary effects on their incidence might be mediated by other influences on hormonal milieu. Third, ecological observations, for example those associating dietary intake of fat with mortality and incidence of breast cancer, have not been sustained in analytical studies on individuals [19]. The interaction between migrant status and age shown for colon cancer incidence in Victoria indicates an increased risk in the migrant population as it ages. This observation is consistent with a late stage effect of migration on colon cancer risk. As noted above, a similar cohort-based pattern has been observed in Italian colorectal cancer mortality [17].

It is interesting to view these trends in light of available information on the risk factors of interest. The principal emphasis in studies of cancer in migrants has been on dietary modification after migration. There is evidence, however, that dietary patterns have also changed in the country of origin. From estimates provided by the FAO in Table 3 concerning per caput nutrient consumption data for Italy and Australia it can be seen that between 1961–1963 and 1983–1985 Italians have consistently obtained more of their energy requirements from vegetable rather than animal foods but that the Italian–Australian ratios have approached unity over time. The same pattern is seen for sources of fats and proteins. Although the total energy requirements of the two peoples should be similar, Australians have historically obtained proportionally more of their energy from animal fats and have eaten greater quantities of fat in the past. Italians have consistently consumed more beta carotene and vitamin C than Australians and this has been unaffected over time. In recent times, Australians have eaten similar quantities of fat to Italians. Italians have increased their total per caput fat consumption by 61% and Australians by 10% between 1961–1963 and 1983–1985. The major change has been in the addition of animal protein and fats (meat) to the Italian diet. Evidence from studies of southern European migrants reveals a similar phenomenon, i.e. on arrival to Australia, Italians and Greeks maintain a cuisine based on complex carbohydrates, vegetables and fruits but enrich it with preferred foods such as meats [20]. Data from the Australian Nutrition Survey conducted in 1983 showed that southern European migrants continued to eat considerably more pasta, tomatoes, citrus fruit, bread, and red wine than Australian born people [21]. Italian migrants to Perth, Western Australia consumed more bread, pasta, fish and red wine, and derived more of their fat from vegetable sources than did Australians [22].

Analytical epidemiological studies have generally provided more support for a relationship between dietary fat and colon cancer than for breast or prostate cancer. On the other hand, a consistent protective effect of fruit and vegetables is reported against cancer of the colon, breast and prostate. The literature on the relationship between fat intake and breast cancer has been reviewed by both schools of thought, and there is still considerable debate [23–25]. The evidence of an association between prostate cancer and fat intake, particularly saturated fat, is much stronger than that between fat intake and breast cancer, and the data are more consistent. There is, however, some inconsistency with regard to beta carotene intake and prostate cancer risk, particularly at older ages [26]. Positive associations between fat and colorectal cancer have been demonstrated in seven case–control studies [27–33] but not in three others [34–36]. Positive associations have also been detected in two cohort studies [37, 38] but not in two others [39, 40]. The association appears stronger for saturated than for unsaturated fatty acids. The intake of saturated fat largely derives from foods of animal origin such as meat and dairy produce. Several recent analytical epidemiological studies lend support to the hypothesis that meat or protein is associated with increased risk of colorectal cancer [29, 38, 41, 42]. Manousos *et al.* [43] demonstrated further that the risk of colorectal cancer associated with a high intake of meat was accentuated in the presence of a low vegetable consumption.

In conclusion, this study provides some evidence of convergence in the incidence of breast and prostate cancer in Italian migrants to Australia to that of the Australian born. The data also provide strong support for a late stage promotional effect of aspects of the Australian human environment on the risk of cancer of the colon. These findings are consistent with ecological trends in dietary intakes, particularly of fat from animal sources.

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A Hepatic Invasive Human Colorectal Xenograft Model

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A hepatic invasive human colorectal xenograft model was derived in nude mice by selection through the liver of the parental cell line, C170. Following intraperitoneal injection, tumours selectively grew on the liver in > 80% of the animals within 15–20 days. The liver-invading xenograft line, renamed C170HM$_2$, had a significantly greater expression of the Lewis^x antigen compared to C170 (mean linear fluorescence per cell > 1000 compared with 500 for C170, $P < 0.02$). C170HM$_2$ had significantly elevated proliferation (when compared with C170) in the presence of epidermal ($P < 0.001$) and basic fibroblast growth factor ($P < 0.001$). C170HM$_2$ also mitogenically responded to type I collagen (derived from rat tails), unlike C170. C170HM$_2$ tumours when invading the liver expressed both interstitial collagenase and gelatinase activity at the invading edge.
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INTRODUCTION

METASTASIS OCCURS in greater than 60% of colorectal cancer patients with the major site of secondary tumour invasion being the liver [1, 2]. Secondary spread of malignant cells is one of the major causes of cancer fatality and can occur even before diagnosis and surgical resection of the original primary tumour [3].

The development of relevant *in vivo* models which allow therapeutic evaluation of potential antimetastatic agents is an important area of research. Experimental metastasis models exist in which colorectal tumour cells are administered intravenously (i.v.) [4–6]. Tumour cells have to survive in the circulation, arrest within an organ and outgrow and invade at a distant site. However, i.v. administration of colorectal tumour cells via the