*Cancer Prevention in Primary Care***Current trends and some prospects for the future—1**

Joan Austoker

This is the first part of the last article in this series looking at how cancer can be prevented in general practice. The final part will be published next week

Cancer control encompasses the whole spectrum from prevention and early diagnosis to treatment and palliation. The key to the future of cancer control will be to establish multidisciplinary approaches to each type of cancer across this spectrum. For primary prevention this requires some understanding of the causes of each cancer. Although understanding of the aetiology of cancer has greatly improved, prospects for the primary prevention of many common cancers remain remote. Other approaches currently under evaluation include chemoprevention and the use of biomarkers. The identification of predisposing genes for some of the common cancers may have a considerable impact on the ability to recognise those at risk. Overall, however, mortality trends indicate that reduction of smoking remains the main priority for cancer prevention in the United Kingdom. For primary care teams, brief interventions to reduce smoking are likely to achieve the greatest benefit. This should be seen as part of broader policies aimed at achieving change in the whole population. The government must acknowledge its major responsibility to cancer prevention by banning all forms of advertising and promotion of tobacco.

Trends in cancer mortality: the importance of smoking

Trends in overall mortality from cancer during 1952-92 show that rates in both males and females increased in elderly people but declined in younger age groups. This divergent pattern is determined mainly by changes in mortality from lung cancer. The proportions of deaths from cancer that are attributed to tobacco are so large (about one third of all such deaths) that the effects of tobacco have dominated trends in overall cancer mortality in men over the past few decades, causing increases where otherwise decreases would have existed, and they are likely to dominate trends in women over the next few decades. If deaths from cancer related to tobacco are discounted there is no evidence that total mortality from cancer is increasing at any age. Non-smokers of all ages seem to have experienced steadily decreasing overall mortality from cancer, together with even more rapidly decreasing mortality from other tobacco related diseases.

Table I shows changes in mortality from lung cancer in England and Wales from 1946 to 1985. Clearly, the generation of men born just after the turn of the century has experienced peak mortality from lung cancer. This can be attributed to the uptake of smoking, which reached its peak earlier in men than in women. Rates for men are now declining signifi-

cantly for all other age groups because fewer men now smoke and cigarettes now contain less tar. In women over 60 the great increase in smoking during and after the second world war is now causing a large increase in the rate of deaths from lung cancer. However, death rates from lung cancer in women are now declining at younger ages so that we can expect a substantial reduction in lung cancer rates in women in the future if this trend continues.

The overall trends in cancer mortality would have been worse had there not been a substantial decrease in mortality from stomach cancer, which has occurred without any deliberate intervention. The reasons for the decline are still unclear. Interesting trends in both incidence and mortality have been observed for several other cancers. I have discussed the increases in prostatic cancer, melanoma, testicular cancer in young men, and cervical cancer in young women in previous articles (issues of 25 June, 23 July, and 30 July). Oesophageal cancer is also becoming more common. It is important to monitor these trends as they may provide clues to the aetiology of these cancers. Overall, however, mortality trends indicate that eradication of smoking remains the main priority for the prevention of cancer in the United Kingdom. I outlined the role of primary care teams in smoking cessation activities in the second article (4 June). A population approach has the greatest potential for reducing morbidity and mortality. The government must therefore acknowledge its major responsibility by banning outright all forms of advertising and promotion of tobacco.

Prospects for primary prevention

The ideal means of effecting cancer control is primary prevention, but this requires some under-

TABLE I—Changes in mortality from lung cancer in England and Wales, 1946 to 1985. The highest rate for each age group is in bold type¹

Age (years)	Death rate per 100 000					% Reduction from peak rate to rate in 1981-5
	1946-50	1956-60	1966-70	1976-80	1981-5	
Men:						
30-34	3.6	3.5	2.5	1.6	1.2	67
40-44	23.6	25.1	21.6	13.8	12.0	52
50-54	95.4	124.8	116.0	99.6	77.0	38
60-64	171.7	331.5	369.5	332.0	300.2	19
70-74	140.0	387.8	621.0	662.5	629.8	5
80-84	76.5	225.8	456.3	762.3	833.6	—
Women:						
30-34	1.2	1.4	1.1	0.8	0.8	43
40-44	4.8	6.0	8.1	6.2	6.0	26
50-54	11.7	16.9	28.4	35.9	30.0	16
60-64	22.1	32.8	51.5	84.6	96.2	—
70-74	31.6	44.5	73.1	110.5	141.9	—
80-84	28.0	45.1	65.7	106.2	135.1	—

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standing of the causes of cancer. By noting differences in the occurrence of cancer between different socio-economic, religious, occupational, and ethnic groups, between sexes and different age groups, between migrants from a community and those who remain behind, and in different time periods, hypotheses on the possible causes of various cancers may be formulated. Table II shows the cumulative incidence rates of some common cancers in the United Kingdom and the percentage reduction in these rates if the lowest observed rate in the world could be achieved in the United Kingdom. This indicates that reductions of over 70% could be achieved for most of the major sites (although some of the reductions may be inflated due to underrecording of cancers in areas with low incidences). There is thus clearly great potential for preventing cancer if the factors responsible for these extreme variations in site specific cancer rates could be

TABLE II—Cumulative incidence rates of common cancers in England and Wales at ages 0-74 compared with those in population with lowest incidence rates worldwide around 1980*

Primary site of cancer	Cumulative incidence (%)		Population	Potential % reduction
	England and Wales	Lowest worldwide*		
Males:				
Lung	9.15	0.66	Madras	93
Stomach	2.23	0.71	Utah	68
Prostate	2.17	0.10	Tianjin, China	95
Bladder	1.99	0.21	Nagpur, India	89
Colon	1.89	0.26	Bombay	86
Rectum	1.60	0.35	Madras	78
Pancreas	0.94	0.12	Madras	87
Females:				
Breast	5.96	1.87	Miyagi, Japan (rural)	69
Lung	2.42	0.05	Nagpur, India	98
Colon	1.65	0.27	Bombay	84
Ovary	1.26	0.41	Tianjin, China	68
Cervix	1.21	0.27	Non-Jews, Israel	78
Endometrium	1.00	0.12	Nagpur, India	88
Rectum	0.90	0.16	Nagpur, India	82
Stomach	0.85	0.31	Utah	64

*Excluding cancer registry data based on small numbers (less than 1 million person years)

TABLE III—Risk factors for various cancers in United Kingdom*

Site†	Incidence (%) in 1988	Mortality (%) in 1992	Risk factor		
			Major established	Minor established	Likely major but unproved
Lung	14.3	23.5	Smoking	Radon, asbestos, polycyclic aromatic hydrocarbons, arsenic Nickel refining, chromates, bischloroethyl ether	Low intake of vegetables rich in β carotene
Large bowel	10.1	11.9		Polyposis coli	Low starch, fibre, and vegetable intake, high fat and/or meat intake
Breast	9.8	9.3	Early menarche, late menopause, late first birth	Postmenopausal obesity	High fat intake, hormones (endogenous and exogenous)
Prostate	4.6	5.8	Black racial group		Hormones (endogenous), high fat intake
Stomach	4.2	5.7	<i>Helicobacter pylori</i> infection, low socioeconomic status, low intake of fresh fruit and vegetables	Blood group A, smoking	High intake of salt and certain preserved foods
Oesophagus	1.9	3.8	Smoking, alcohol		Very hot drinks, low intake of fruit and vegetables
Ovary	1.9	2.6	Early menarche, late menopause, low parity, oral contraceptives (protective)		
Cervix	1.6	1.1	Human papillomavirus (specific types only), multiple sexual partners, low socioeconomic status	High parity	Smoking, genital hygiene
Skin (melanoma)	1.5	0.8	Sun or other ultraviolet light, benign melanocytic naevi, white racial group	Xeroderma pigmentosa	Sunburn
Endometrium	1.4	0.6	Early menarche, late menopause, low parity, obesity, exogenous oestrogens (in absence of progestogens), combined oral contraceptives (protective)		
Skin (non-melanoma)	11.9	0.3	Sun or other ultraviolet light, white racial group	Arsenic, polycyclic aromatic hydrocarbons, xeroderma pigmentosa	
Testis	0.5	0.08	White racial group	Undescended testis	Fetal exposure to endogenous hormones

*Adapted from Pike and Forman¹; D Forman (personal communication).

†In order of decreasing contribution to mortality.

identified, and if people could be persuaded to adopt the appropriate low risk behaviour patterns. Likewise, comparisons of age standardised rates between countries suggest that some 80-90% of the current total cancer rate in the United Kingdom is caused by environmental or behavioural factors, or both.

KNOWN AND SUSPECTED RISK FACTORS

Table III summarises the known and suspected risk factors for some cancers in order of the percentage of all cancer deaths caused by the tumour in the United Kingdom in 1992 (D Forman, personal communication). The established risk factors have been divided into major and minor categories in terms of their importance to the total cancer burden in the United Kingdom for the specific site.

Over half of all mortality from cancer is accounted for by cancers of the lung, large bowel, breast, and stomach. Although, scientifically, there will be benefits from understanding the aetiological factors for an uncommon cancer, preventing part or even all of the mortality from such a cancer will have only a small impact on total cancer mortality. Minor risk factors for a common cancer may have a much greater public health significance than major risk factors for rarer forms of cancer.

Table IV gives some indication of the scope for prevention. Whether to implement a prevention strategy will depend on the strength of evidence relating a particular risk factor to the development of cancer. It will also relate to the feasibility of reducing the risk—for example, although reproductive factors such as age at first birth and number of children may account for some 7% of mortality from cancer in women, manipulating these risk factors is not practical. If the reduction of a risk factor is a realistic possibility on a population basis, evidence must exist of the effectiveness of specific intervention strategies. As I discussed in the first article in this series (28 May), any health promotion measure in primary care must be subjected to rigorous scientific evaluation before it is

TABLE IV—*Proportions of cancer deaths attributable to various factors**

Factor or class of factors	% Of all cancer deaths	
	Best estimate that potentially could be avoided	Range of acceptable estimates
Diet	35	10-70
Tobacco	30	25-40
Reproductive factors and sexual behaviour	7	1-13
Occupation	4	2-8
Alcohol	3	2-4
Geophysical factors	3*	2-4
Pollution	2	<1-5
Medicines and medical procedures	1	0-5-3
Food additives	<1	-5†-2
Industrial products	<1	<1-2
Infection	10?	1-?

*Only about 1%, not 3% could reasonably be described as "avoidable." Geophysical factors also cause a much greater proportion of non-fatal cancers (up to 30% of all cancers, depending on ethnic mix and latitude) because of the importance of ultraviolet light in causing the relatively non-fatal basal cell and squamous cell carcinomas of skin exposed to sunlight.

†Allowing for a possible protective effect of antioxidants and other preservatives.

introduced and the necessary skills to implement the intervention must be disseminated to primary care teams. I have reviewed the evidence for helping patients to stop smoking, reduce alcohol intake, and avoid excessive exposure to the sun in this series. Whereas dietary modifications could perhaps avoid a greater number of cancer deaths than could changes in smoking patterns, their role in human carcinogenesis is less well defined. There are very few changes (other than to increase the consumption of fruit and vegetables) that could be implemented on the basis of current understanding of diet and cancer.

CHEMOPREVENTION

Although understanding of the aetiology of cancer has greatly improved, prospects for the primary prevention of many common cancers such as breast cancer remain remote. Likewise, although treatment has become more rational, progress is very slow and has had only a modest impact on death rates. Chemoprevention is a fairly new approach being investigated and consists of interventions performed during the neoplastic process up to the stage of in situ carcinoma. Several potential chemopreventive agents are currently under investigation, including retinoids for preventing head, neck, and lung cancers and tamoxifen for breast cancer.

Tamoxifen has emerged as the main endocrine treatment for all stages of breast cancer. About 50% of women with metastatic breast cancer benefit from tamoxifen. Furthermore, the addition of this drug to other treatments reduces both the recurrence and mortality rates from early stages of disease, and it reduces the risk of a new primary cancer developing in the contralateral breast by 40%. Preliminary data on blood lipid concentrations and bone mineral metabolism suggest that additional benefits in reducing the incidence of ischaemic heart disease and osteoporosis might also be expected.

The possibility of using tamoxifen to prevent or delay development of breast cancer in women with a clinically significant family history of breast cancer is the subject of continuing debates on the balance of potential risks and benefits. Concern has been expressed that tamoxifen may promote the production of liver and, in particular, endometrial cancers. Tamoxifen produces liver tumours in rats during high dose, long term administration. There are no data, however, to suggest that tamoxifen used in doses given in adjuvant clinical trials increases the incidence of liver cancer in women. Clinical evidence from randomised trials suggests, however, that there is an increased risk of women developing endometrial

cancer if tamoxifen is taken at a dose of 20 mg a day.

Performing clinical trials on the chemoprevention of breast cancer raises complex methodological and ethical issues. Even mild toxicity may be unacceptable in the general population, but if a high risk population can be identified the benefits may well justify the risks. To address the issue effectively, the magnitude of the problem of breast cancer in terms of its incidence and mortality has to be considered.

Results from a pilot study at the Royal Marsden Hospital indicate that the potential benefits of using tamoxifen in a prevention trial in healthy women with a strong family history of breast cancer far outweigh the potential risks. Ultimately, a clinical trial is the only way to identify overall benefit and harm. Tamoxifen prevention trials are now underway in Europe and the United States, and a trial has just started in the United Kingdom (using tamoxifen at 20 mg a day for at least five years). This study is recruiting women aged 45 to 65 who have a greater than twofold risk of developing breast cancer and those aged 35 to 44 years who have at least a tenfold risk. A study is also assessing any negative psychosocial impact of tamoxifen in healthy women.

VIRUSES

Viruses are responsible for about 15% of cancers worldwide. If measures could be found to control infections caused by viruses such as hepatitis B, human papillomavirus and Epstein-Barr virus a significant proportion of human cancer could be prevented. The production of vaccines against human oncogenic viruses is, however, far from straightforward. In many cases the role of the virus in tumour production is uncertain. Infection by these viruses is not in itself sufficient to induce cancer and several other factors are implicated in the process. Also, tumour production may be a rare outcome of infection by a widespread and not very pathogenic virus.

A vaccine against the hepatitis B virus is already available, and a long term intervention study is being conducted in the Gambia, aimed at evaluating the effectiveness of hepatitis B vaccination in the prevention of primary hepatocellular carcinoma. The possibility of developing an immunising vaccine against human papillomavirus, which is of greater relevance to the prevention of cancer in the United Kingdom, is still in its infancy. Certain strains of human papillomavirus (types 16, 18, 31, and 33) seem to be causally related to cervical cancer. Viral DNA, particularly that of human papillomavirus 16 and, to a lesser extent, type 18, is found in over 80% of tumour biopsy specimens and in the higher grades of cervical intraepithelial neoplasia. The mechanism linking human papillomavirus with cervical carcinoma is poorly understood. Infection with the virus is not in itself sufficient for transformation of epithelial cells. Exposure to still ill defined cofactors is additionally necessary to promote progression to cancer of lesions associated with the virus. Smoking, hormonal factors, oral contraceptives, infection by other sexually transmitted viruses or micro-organisms, and genetic predisposition may all play a part. The problems of developing a safe and effective prophylactic vaccine against human papillomavirus and delivering it to a susceptible population before they become infected point to the need for other approaches. An alternative is to limit infection, usually after it is clinically evident, with a therapeutic vaccine primarily concentrating on the induction of a specific cell mediated immune response which would lead to regression of pre-cancerous lesions.

Ultimately, it may prove possible to improve the management of women who have mildly dyskaryotic smear test results or low grade cervical intraepithelial

neoplasia by testing for the high risk virus types which have been associated with lesions which progress to high grade cervical intraepithelial neoplasia and carcinoma. The hope is that further elucidation of the molecular mechanism that leads to high grade cervical intraepithelial neoplasia will identify those features of viral expression and integration, as well as the aberrations of cellular oncogenes or tumour suppressor genes, that are relevant to progression to carcinoma.

Understanding and preventing tumour progression

Carcinogenesis is a multistage process. The first stage is known as initiation and is followed by one or more promoting events. Many potentially carcinogenic agents are present in our diet and environment.

Little is known about the factors that govern the fate of precancerous lesions and determine whether a cancer develops and progresses. With cigarette smoking, components of the smoke are thought to promote development of lung cancer in the later stages of carcinogenesis. This tumour progression phase can be retarded by stopping smoking, however long ago the habit was established. In the future, modifications in diet or hormonal status may also be effective in suppressing proliferation and thereby preventing progress to cancer in subjects with precancerous lesions of particular tissues or in those in a high risk group for cancer development.

Central to progress is the need for a clear understanding of the complex biology of the early stages of cancer development and progression. Mechanisms responsible for the control of normal proliferation and differentiation of the various cell types in the body will allow a greater insight into the abnormal growth of malignant cells. Much more needs to be done to identify potential promoting agents for the common cancers and thus the means for intervention in the process of tumour progression.

Over the past decade the emergence of a more

coherent picture of the molecular progression of epithelial carcinogenesis from initiation to promotion has provided the opportunity for developing rational approaches to cancer control. The use of biomarkers, defined as morphological or molecular alterations occurring between initiation and tumour invasion, can have a number of applications for the management of individuals with cancer, or those at risk of developing cancer. A single biomarker, or panels of biomarkers, when rationally assembled, may be used to establish the state of a tissue and provide a clear picture of the state of cancer progression. Biomarkers can be used to help elucidate questions of aetiology and pathogenesis of disease and to refine the understanding of the relations between exposure variables and disease outcomes. Biomarker analysis could also be used in a variety of other cancer related applications, including risk (or susceptibility) assessment, early detection, prognostic discrimination, and disease progression, as well as intermediate end point determination of whether there is progression—for example, in prevention trials which require prolonged follow up.

- 1 Pike MC, Forman D. Epidemiology of cancer. In: Franks LM, Teich NM, eds. *Introduction to the cellular and molecular biology of cancer*. Second edition. Oxford: Oxford University Press, 1991:49-97.
- 2 Doll R, Peto R. *The causes of cancer*. Oxford: Oxford University Press, 1981.

The concluding part of this article will be published next week.

Correction

Screening for cervical cancer

An editorial error occurred in this article, the seventh in the series on cancer prevention in primary care by Joan Austoker (23 July, pp 241-8). The first sentence in the penultimate paragraph under the heading "Interpreting and managing results of smear tests" should have read: "In practice, mild and moderate dyskaryotic smear test results do not correlate well with the histological diagnosis of mild or moderate dysplasia—that is, grade I or II cervical intraepithelial neoplasia."

A MEMORABLE PATIENT

"I'm willing to come for your research"

The surgeon's interview with patient and spouse after cancer surgery usually has a rare blend of intimacy, tension, and poignancy. This one was no exception. The patient had been expecting the worst: the significance of the painless jaundice and recent weight loss had not been lost on him. So he took the news calmly, but not too bravely as evidenced by the tight grip he had on his wife's hand. His retirement, recently started, was obviously not destined to be a long one. He thoughtfully gave me absolution for my medical impotency to cure him, reassuring me that the combination of his faith in God and the devotion of his wife would enable him to face anything, even death.

Discharged early on the fifth day after the operation, the palliative procedure seemed to give him a new, if temporary, lease on life. His first visit came and went; the celebrations of his 40th wedding anniversary reportedly raised quite a stir in the small country town where he lived 100 km from the university department of surgery.

At the time, some colleagues and I were recruiting cancer patients who were losing weight for a study of cancer cachexia.¹ The subjects were asked to undergo a two hour ordeal consisting of a hyperinsulinaemic euglycaemic clamp (intravenous infusions of glucose and insulin) and indirect calorimetry where respiratory gas exchange was measured using a ventilated hood canopy. The project was funded by a grant from the New Zealand Cancer Society and, somewhat parochially, the regional daily newspaper had deemed this newsworthy and carried a short paragraph on the research project.

Several months later I received a letter from my patient. Near death and even too weak to hold a pen, he said via his wife's transcription:

"I apologise that I am not well enough to keep my next outpatient clinic appointment with you—it is simply too far to come. However, I saw your cancer research project reported in the newspaper and if I can help in any way, I'm willing to come for your research."

He never did—nor could he have, of course. As it was, my reply letter by return mail gently declining his offer reached him just before he died.

He exemplifies the many patients who, in addition to the trials of their illnesses, are prepared to enrol in research studies with cheerfulness, courage, and not a little personal inconvenience. The detached style we conventionally use in reporting scientific work is out of place when acknowledging the debt we owe to these willing collaborators.

I offer this as a tribute to my memorable patient's memory and to all others like him.—BRYAN PARRY is a consultant surgeon in Singapore

1 McCall JL, Tuckey JA, Parry BR. Serum tumour necrosis factor alpha and insulin resistance in patients with gastrointestinal cancer. *Br J Surg* 1992;79:1361-3.

We are delighted to receive submissions of up to 600 words on *A paper (or patient or book) that changed my practice, A memorable patient, The one message I would like to leave behind, or related topics.*