Cancer Control In Women. Update 2003[1]

P BOYLE, ME LEON, P MAISONNEUVE and P AUTIER

SUMMARY

The global cancer burden in women appeared to be increasing quickly at the end of the twentieth century with notable increases in the absolute numbers of cases of breast, cervix, lung and colorectal cancer of concern. However, prospects for cancer control in women appear to be good within our current knowledge and deserve close attention. Rates of lung cancer in women are increasing substantially in many countries and seem set to overtake breast cancer as the commonest form of cancer death in women in many parts of the world. These changes are due to the effects of cigarette smoking, a habit which women widely embraced during the second half of the last century. The high levels of smoking current in young women, which have yet to have their full impact on death rates, constitute an important hazard not only for future cancer risks but for several other important causes of death.

Although the breast is the commonest form of cancer in women in most western countries, the etiology of this disease remains elusive and preventable causes remain to be identified. Endogenous hormones also appear to have a role in cancer risk in women: oral contraceptives seem to increase slightly the risk of breast cancer in users in the use, and in the immediate post-use, period, but ten years after cessation the risk returns to that of never users. Oral contraceptive usage also appears to be protective against ovarian and endometrial cancer. The use of Hormonal Replacement Therapy (HRT) appears to increase the risk of endometrial cancer and a positive association with breast cancer risk appears to exist.

Within our current knowledge of the epidemiology of cancer in women, the most important Cancer Control strategy is the prevention of cigarette smoking and the increase in the prevalence of adult women quitting smoking. Screening has also shown to be effective in reducing incidence and mortality of cervix cancer and mortality from breast and colorectal cancer. Although more work is needed, it is becoming clear that there could be an important role of HPV testing to further enhance cervix cancer screening.

Key-words: Cancer Control; Cancer Prevention; Tobacco; Screening.

In previous versions of this invited article, attention has focussed on describing the cancer burden in women world-wide and in an exposition of risk factors.[1,2] Much of what was written previously still applies and there is little point in providing another description of the epidemiological situation. Attention is gradually moving to focus on cancer prevention and mortality reduction, i.e. on Cancer Control.[3] In view of what is known about Cancer Etiology in women, in this article a brief outline of strategies and priorities for Cancer Control will be provided.

CANCER IN WOMEN WORLD-WIDE

It has been estimated that in the year 2000 there were approximately ten million new cases of cancer diagnosed throughout the world: this omits non-melanoma skin cancers. Of this total, slightly under one-half were in women. The most frequent form in women was breast cancer with over one million new cases diagnosed annually (Table 1). To many observers in western countries, it will be somewhat surprising to see that there were 470,000 cases of cervix cancer each year and that this was the second commonest form of cancer in women world-wide. The global cancer burden in women appears to have increased during the last decade according to these recent estimates available. It is of concern to see the increases taking place again in the numbers of new cases of cervix cancer (from 370,000 in 1990 to 470,000 in 2000). The continual rise in the numbers of cases of colorectal cancer is also of concern as is the continual increase in the numbers of new cases of lung cancer (Table 1).

Cancer of the Breast

Globally, breast cancer is the most frequent malignancy among women, with an estimated 1,050,000 new cases in 2000. The highest incidence rates of breast cancer are (generally) reported from North America and other high-resource countries (Table 2). The lowest incidence rates are concentrated in regions of low-resource countries although it is increasingly clear that there is no part of

[1] Authors' Note: We were invited to contribute this article which is an updated version of articles previously published in the Journal of Epidemiology and Biostatistics (1998; 3:137–168) and in the International Journal of Gynecology and Obstetrics (2000; 70:263–303): we do so with the publishers permission. We acknowledge the large amount of similarity between these two articles and a more recent article published in the Annals of Oncology (2003; 14:973–1005) and do not in any way claim that these are independent. This work merely updates the previous articles. July, 2003.

Correspondence to: Prof. P. Boyle, Dept. of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141, Milan, Italy; phone: +39-0257489816, fax: +39-0257489922, e-mail: director.epi@ieo.it

Table 1
Estimated annual cancer incidence burden worldwide in women in 1975, 1980, 1985, 1990 and 2000

Site	Year									
	1975		1980		1985		1990		2000	
Mouth and pharynx	105,600	(6)	121,200	(8)	142,800	(7)	105,400	(11)	138,000	(9)
Esophagus	102,300	(7)	108,200	(9)	107,600	(10)	103,200	(9)	133,300	(10)
Stomach	260,600	(3)	260,600	(4)	282,300	(4)	287,200	(4)	317,900	(5)
Colorectal	255,600	(4)	285,900	(3)	346,500	(3)	381,000	(2)	446,000	(3)
Liver	76,700	(9)	79,500	(12)	100,700	(11)	121,100	(8)	166,000	(8)
Lung	126,700	(5)	146,900	(6)	219,300	(5)	265,100	(5)	337,100	(4)
Breast	541,200	(1)	572,100	(1)	719,100	(1)	795,600	(1)	1,050,300	(1)
Cervix uteri	459,400	(2)	465,600	(2)	437,300	(2)	371,200	(3)	470,600	(2)
Corpus uteri	–		148,800	(5)	140,000	(8)	142,400	(7)	189,000	(7)
Ovary	–		137,600	(7)	161,500	(6)	165,500	(6)	192,400	(6)
Lymphoma	91,300	(8)	98,000	(10)	135,200	(9)	116,300	(10)	120,800	(11)
Leukemia	75,400	(10)	81,300	(11)	95,500	(12)	100,900	(12)	112,800	(12)
All sites	2,901,800		3,100,000		3,774,200		3,789,800		4,737,600	

Sources: Estimates of the global cancer burden have been made for 1975 (Parkin, Stjernsward and Muir, 1984), 1980 (Parkin, Laara and Muir, 1988), 1985 (Parkin, Pisani and Ferlay, 1993), 1990 (Parkin, Pisani and Ferlay, 1998) and 2000 (Parkin, Bray, Ferlay and Pisani 2001): these estimates are for all forms of cancer excluding non-melanoma skin cancers.[116–120]

Table 2
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the breast in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Lowest Incidence Rates**		
Uruguay, Montevideo (1993–1995)	3679	114.9	India, Trivandrum	504	19.7
USA, Ca, San Fco: Non-Hispanic White	9376	109.6	India, Ahmedabad	1165	19.1
USA, Ca, Los Angeles: Non-Hispanic White	15291	103.9	Korea, Busan (1996–1997)	822	18.6
USA, Hawaii: Hawaiian	493	101.3	China, Wuhan	2115	18.1
USA, Hawaii: White	985	101.1	Thailand, Lampang	376	17.0
Israel, Jews born in Europe/America	6865	98.5	Thailand, Chiang Mai	618	16.1
USA, Connecticut: White	11579	97.7	India, Karunagappally	148	15.0
USA, Georgia, Atlanta: White	5009	97.6	Viet Nam, Ho Chi Minh City (1995–1998)	1156	13.6
Switzerland, Geneva	1516	97.0	Korea, Kangwha County	29	12.7
USA, Washington, Seattle	12190	96.0	Oman, Omani	243	12.7
USA, New Jersey: White	25344	95.5	Thailand, Songkhla (1993–1996)	253	11.7
USA, SEER[b]: White	67272	92.1	Thailand, Khon Kaen	445	10.8
USA, New York State: White	51612	90.6	China, Qidong County	328	10.0
USA, New Mexico: Non-Hispanic White	3071	90.3	China, Jiashan	108	9.1
Israel, Jews born in Israel	2744	89.5	The Gambia (1997–1998)	41	7.0

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.
[b] The Surveillance, Epidemiology and End Results (SEER) is a set of geographically defined, population-based, central cancer registries in the United States.

Table 3
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the cervix in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Lowest Incidence Rates**		
Zimbabwe, Harare: African	613	55.0	Japan, Yamagata Prefecture	245	4.7
Uganda, Kyadondo County	465	41.7	Italy, Macerata Province	53	4.7
Brazil, Goiânia (1995–1998)	646	38.2	USA, Hawaii: Japanese	51	4.5
Mali, Bamako (1994–1996)	182	35.9	Kuwait: Kuwaitis (1994–1997)	34	4.2
Argentina, Concordia	107	30.6	Switzerland, Basel	73	4.1
India, Chennai	2358	30.1	Finland	811	4.0
The Gambia (1997–1998)	171	29.8	China, Wuhan	433	3.9
Colombia, Cali (1992–1996)	1102	29.8	USA, Hawaii: Chinese	11	3.8
Viet Nam, Ho Chi Minh City (1995–1998)	2289	28.8	Spain, Navarra	72	3.7
Ecuador, Quito	675	26.0	Spain, Cuenca	26	3.4
India, Delhi (1993–1996)	2983	25.8	Israel: Non-Jews	39	2.5
Thailand, Chiang Mai	974	25.3	China, Tianjin	311	2.4
China, Taiwan (1997)	2855	24.9	China, Shanghai	612	2.3
Thailand, Lampang	531	24.2	China, Qidong County	79	2.2
India, Bangalore	1765	23.5	China, Jiashan	14	1.2

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.

the world where there is a truly low rate of breast cancer anymore.

Cancer of the Cervix

Cancer of the cervix, choriocarcinoma, and cancer of the corpus uteri are generally well separated in incidence statistics and analytical studies. Cancer of the cervix is the second most common form of cancer in women worldwide, with about 80 per cent of these cancers occurring in low- and medium-resource countries. It is the leading cancer in women in sub-Saharan Africa, Central and South America, and South-East Asia. The highest incidence rates are reported from regions of the world in low-resource countries (Table 3). Low incidence rates of cervix cancer are found in a variety of population settings in low-, medium- and high-resource regions (Table 3).

The highest incidence rates recorded previously around 1980 were in Recife in Brazil (83.2 per 100,000) and in the Pacific Polynesian Islanders (64.4); these rates are somewhat higher than the current highest (55.0 in Zimbabwe). Incidence rates are intermediate in Central and Eastern Europe, but much lower in North America, Australasia and Northern and Western Europe. In Europe, low rates are noted in Finland, Switzerland, Spain and southern Italy. In the United States large differences are seen between ethnic groups, with a twofold difference between the black and white populations. Incidence is also lower in Japanese populations and Chinese populations. Ethnic differences are also seen in New Zealand between the Maoris, the non-Maoris, and the Pacific Polynesian Islanders. Urban populations frequently show higher rates than rural populations.

Cancer of the Corpus Uteri

The highest rates of cancer of the corpus uteri are reported from the United States and Canada, generally from populations which have a white predominance (Table 4). The highest incidence rate (26.6 per 100 000) is reported from the Hawaiian population of Hawaii. Low incidence rates are reported from populations of India, South-East Asia and Africa (Table 4).

Individual mortality statistics for cancer of the cervix and endometrium are generally unreliable. Thus it is necessary to consider uterine cancer as a single entity when discussing mortality data and investigating temporal trends: for completeness, the incidence rates of all uterine cancers are presented (Table 5).

Cancer of the Ovary

Ovarian cancer is a moderately frequent disease representing the most frequent cause of death from gynecological malignancies in the Western world. It is the

Table 4
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the uterus (including endometrium) in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Lowest Incidence Rates**		
USA, Hawaii: Hawaiian	129	26.6	Algeria, Algiers	82	2.2
USA, Connecticut: White	2446	20.7	Korea, Seoul	569	2.2
USA, Ca, Los Angeles: Non-Hispanic Whites	3157	20.3	Thailand, Khon Kaen	86	2.2
USA, Ca, San Fco: Non-Hispanic Whites	1830	20.2	The Gambia (1997–1998)	10	2.1
USA, New Jersey: White	5294	20.0	Korea, Daegu (1997–1998)	55	2.1
USA, Iowa	2242	19.2	China, Jiashan	20	1.9
USA, Washington, Seattle	2411	18.6	Korea, Kangwha County	5	1.9
USA, SEER: White	13641	18.4	Thailand, Songkhla (1993–1996)	37	1.9
USA, Michigan, Detroit: White	2192	18.4	Mali, Bamako (1994–1996)	8	1.7
USA, New York State: White	10367	18.2	China, Wuhan	174	1.6
Czech Republic	7748	18.2	Viet Nam, Hanoi	75	1.6
Canada, Manitoba	747	17.9	Korea, Busan (1996–1997)	64	1.5
Slovakia	3186	17.1	China, Qidong County	44	1.4
USA, Utah	898	16.5	India, Ahmedabad	74	1.4
USA, Georgia, Atlanta: White	820	16.3	India, Karunagappally	8	0.9
Malta	215	16.3	Oman, Omani	9	0.5

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.

Table 5
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the uterus (including cervix uteri, corpus uteri and uterus unspecified) in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Lowest Incidence Rates**		
Zimbabwe, Harare: African	640	54.4	Pakistan, South Karachi (1995–1997)	133	12.8
Uganda, Kyadondo County	487	46.8	Spain, Albacete	157	12.7
Brazil, Goiânia (1995–1998)	714	43.7	France, Manche (1994–1997)	178	12.7
Argentina, Concordia	146	43.6	USA, New Mexico	962	10.4
Mali, Bamako (1994–1996)	198	39.8	Japan, Osaka Prefecture	3240	10.4
Colombia, Cali (1992–1996)	1138	34.3	Japan, Miyagi Prefecture	809	10.1
Czech Republic	11855	33.2	Oman, Omani	178	9.1
Slovakia	5483	32.9	Japan, Yamagata Prefecture	412	8.9
India, Chennai (Madras)	2481	32.5	Kuwait (1994–1997)	134	8.8
Poland, Kraków	878	32.5	China, Tianjin	800	6.6
Uruguay, Montevideo (1993–1995)	829	31.1	China, Shanghai	1435	6.4
Viet Nam, Ho Chi Minh City (1995–1998)	2372	31.0	China, Beijing	466	6.0
Ecuador, Quito	728	30.2	China, Wuhan	593	5.6
Philippines, Manila	2455	29.8	China, Qidong County	125	4.0
Yugoslavia, Vojvodina	2258	29.8	China, Jiashan	39	3.7

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.

Table 6
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the ovary in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Lowest Incidence Rates**		
Switzerland, St. Gall-Appenzell	322	16.3	India, Trivandrum	116	4.5
Iceland	130	16.2	Viet Nam, Hanoi	230	4.5
Israel: Jews born in Europe or America	1002	16.0	Thailand, Songkhla	95	4.3
Sweden	5377	15.2	Viet Nam, Ho Chi Minh City (1995–1998)	368	4.1
UK, England, Oxford Region	1452	15.1	China, Tianjin	479	4.0
UK, England, North Western	2319	14.5	Israel: Non-Jews	72	4.0
USA, Hawaii: White	136	14.4	Thailand, Lampang	79	3.7
USA, New Jersey: White	3786	14.4	India, Ahmedabad	217	3.6
USA, Washington, Seattle	1805	14.2	China, Wuhan	366	3.3
Czech Republic	5713	14.2	Oman, Omani	66	2.8
UK, England, East Anglia	1257	14.0	India, Karunagappally	26	2.5
USA, California, San Fco: Non-Hispanic White	1205	14.0	Argentina, Concordia	47	2.4
UK, Scotland	3055	13.9	China, Jiashan	27	2.3
UK, Northern Ireland	798	13.8	The Gambia (1997–1998)	12	2.1
USA, New York State: White	7802	13.8	France, La Reunion (1993–1994)	13	2.0
			China, Qidong County	48	1.5

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.

sixth most frequent form of cancer in women worldwide with an estimated 192,000 incident cases in 2000 (Table 1). Epithelial cystadenocarcinomas constitute the large majority of ovarian malignancies. The less frequent germ-cell tumors have a younger age distribution. The range of geographical variation for this disease is increasing.

The highest incidence rates of cancer of the ovary are reported among a variety of European and North American population groups. The lowest rates are frequently found in Asian population groups (Table 6). Most rates in Europe and North America range between 10 and 14. Rates for blacks American women are about two-thirds of those for white women. Although women in Asia have a relatively low incidence of ovarian tumors (in the range 5–7), Chinese and Japanese who reside in the United States tend to have slightly higher rates although less than those in the white population.

Cancer of the Vulva, Vagina and other female genital organs

There are some parts of the world where cancers of these types are not so rare (Table 7) although there has been relatively little epidemiological study of these forms of cancer and it is difficult to characterize the regions of the world with either high or low rates of these forms of cancer.

CANCER CONTROL

The diseases grouped under the title *Cancer* are remarkably common and of major Public Health importance since approximately half the people who develop cancer die from their disease. Thus the concept of Cancer Control has been developed to approach the cancer problem at various points in its evolution with the overall goal of reducing cancer suffering and death.

The most obvious ways to prevent people dying from cancer are either to find cures for the different forms of the disease or to find ways to stop the development of clinical cancer in the first instance. At the present time, cancer prevention involves determining the causes of cancer (risk determinants) among those factors shown to be associated with the development of the disease by epidemiological studies (risk factors). Avoiding or reducing exposure to risk determinants would result in a reduction in cancer risk.

The evidence that cancer is preventable is compelling. Different populations around the world experience different levels of different forms of cancer[4] and these levels change with time in orderly and predictable manners[5].

Table 7
Annual, age-standardized incidence rates per 100,000 person-years of cancer of the vulva, vagina and other female genital organs in international populations circa 1995[a]

Registry	Cases	ASR	Registry	Cases	ASR
Fifteen Highest Incidence Rates			**Fifteen Highest Incidence Rates**		
China, Hong Kong	1289	7.5	India, Trivandrum	14	0.6
Australia, Northern Territory	16	5.5	Japan, Hiroshima (1991–1995)	22	0.6
Poland, Lower Silesia	456	4.5	Korea, Busan (1996–1997)	23	0.6
Brazil, Campinas (1991–1995)	81	4.2	Thailand, Khon Kaen	21	0.6
Algeria, Algiers	139	3.6	China, Shanghai	121	0.5
Italy, North East (1995–1997)	180	3.3	Oman, Omani	9	0.5
Italy, Venetian Region (1993–1996)	202	3.1	Japan, Saga Prefecture	17	0.5
Portugal, Vila Nova de Gaia	21	2.8	Japan, Osaka Prefecture	129	0.4
Austria, Tyrol	62	2.7	Japan, Miyagi Prefecture	36	0.4
Austria, Vorarlberg	30	2.7	Korea, Kangwha County	1	0.4
Yugoslavia, Vojvodina	228	2.7	China, Jiashan	4	0.3
Switzerland, Ticino (1996–1997)	12	2.6	Mali, Bamako (1994–1996)	2	0.3
Brazil, Goiânia (1995–1998)	39	2.4	Kuwait (1994–1997)	4	0.3
Zimbabwe, Harare: African	16	2.4	Japan, Yamagata Prefecture	12	0.2
Norway	343	2.4	China, Qidong County	3	0.1

[a] Data are for the period 1993–1997 unless otherwise specified. Source: abstracted from Parkin et al, 2002.

Groups of migrants quickly leave behind the cancer levels of their original home and acquire the cancer pattern of their new residence sometimes within one generation.[6,7] Thus those Japanese who left Japan for California left behind the high levels of gastric cancer in their homeland and exchanged it for the high levels of breast and colorectal cancer present among inhabitants of their new home. Furthermore, groups whose lifestyle habits differentiate themselves from other members of the same community frequently have different cancer risks.

For reasons such as these, it is estimated that upwards of 80 per cent, or even 90 per cent, of cancers in western populations may be attributable to environmental causes[8] defining "environment" in its broadest sense to include a wide range of ill-defined, dietary, social and cultural practices. Although all of these avoidable causes have not yet been clearly identified, it is thought that risk determinants exist for about one half of cancers (Table 8). Thus, primary prevention in the context of cancer is an important area of Public Health.

Table 8
Estimate of the proportion of cancer deaths that will be found to be attributable to various factors[a]

	Best estimate	Range
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food additives	<1	5–2
Sexual behavior	1	1
Yet to be discovered hormonal analogies of reproductive factors	Up to 6	0–12
Occupation	4	2–8
Pollution	2	1–5
Industrial products	<1	<1–2
Medicines and procedures	1	0.5–3
Geographical factors	3	2–4
Infective processes	10	1-?

[a]Refers to United Kingdom or United States cancer pattern, Source: Peto (1985).

It is very frequently the case that the probability of successful treatment of cancer is increased, sometimes very substantially, if the cancer can be diagnosed at an early stage. Awareness of the significance of signs and symptoms is important, but all too frequently cancers which exhibit symptoms are at an advanced stage. *Screening* is a term frequently applied to the situation where tests are used to indicate whether an (generally asymptomatic) individual is at a high or low chance of having a cancer. Detecting cancers at an

Table 9
European Code Against Cancer (third version). Abstracted from Boyle et al (2003)[3]

Many aspects of general health can be improved and many cancer deaths prevented, if we adopt healthier lifestyles:

1. Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
2. Avoid obesity.
3. Undertake some brisk, physical activity every day.
4. Eat a variety of vegetables and fruits every day: eat at least five portions daily. Limit your intake of foods containing fats from animal sources.
5. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.
6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life
7. Comply strictly with regulations aimed at preventing occupational or environmental exposure to known cancer-causing substances. Follow advice of National Radiation Protection Offices.

There are Public Health programs which could prevent cancers developing or increase the probability that a cancer may be cured:

8. Women from 25 years of age should participate in cervical screening. This should be within programs with quality control procedures in compliance with "European Guidelines for Quality Assurance in Cervical Screening".
9. Women from 50 years of age should participate in breast screening. This should be within programs with quality control procedures in compliance with "European Guidelines for Quality Assurance in Mammography Screening".
10. Men and women from 50 years of age should participate in colorectal screening. This should be within programs with built-in quality control procedures.
11. Participate in vaccination programs against Hepatitis B Virus infection.

early, asymptomatic stage could lead to decreases in the mortality rate for certain cancers.

An obvious way to prevent cancer death is to cure those cancers which develop. However, there have been few major breakthroughs in cancer treatment in the sense of turning a fatal tumor into a curable one. Notably successes have been in Testicular Teratoma[9], Hodgkin's Disease[10], Children's Leukemia, Wilm's Tumor and choriocarcinoma. Progress in survival of the major cancers has been very much less than hoped. Adjuvant chemotherapy and Tamoxifen have improved survival in breast cancer[11], adjuvant chemotherapy has also contributed to improvements in prognosis of ovarian cancer and colorectal cancer and there have been some other progress which could be attributed specifically to certain treatments.

General progress in medical science has led to modern anesthesia making more patients to be candidates for surgery and surgery safer, better control of infection and bacterial diseases, better imaging has improved tumor localization and staging, and better devices are available to deliver the appropriate doses of radiation and drugs. Thus, more patients can get better and more appropriate therapy and, hence, have a better prognosis.

The quality-of-life issue has not been neglected with breast conservation therapy now almost supplanting traditional, radical mastectomy in the majority of women; more plastic breast reconstruction; less amputation of limbs for bone and soft-tissue sarcomas; and better colostomies, being some important advances.

Against this background of Cancer as an important Public Health problem which is one of the commonest causes of premature and avoidable death in Europe, the **European Code Against Cancer** was introduced to be a series of recommendations which, if followed, could lead in many instances to a reduction in cancer incidence and also to reductions in cancer mortality.[3,12] This most recent revision[3] will form the basis for Cancer Control in Women described herein.

Any recommendation made to reduce cancer occurrence should not be one which could lead to an increased risk of other diseases. The recommendations which comprise the revised *European Code Against Cancer* should, if followed, also lead to improvements in other aspects of general health (Table 9). It is also important to recognise from the outset that each individual has choices to make about their lifestyle some of which could lead to a reduction in their risk of developing cancer. These choices, and the rationale underlying their recommendation, are presented below.

Tobacco Smoking

It is estimated that between 25 and 30% of all cancers in developed countries are tobacco-related[13,14]. From the results of studies conducted in Europe, Japan and North America, between 87 and 91% of lung cancers in men, and between 57 and 86% of lung cancers in women, are attributable to cigarette smoking. For both sexes combined the proportion of cancers arising in the esophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol are between 43 and 60%. A large proportion of cancers of the bladder and pancreas and a small proportion of cancers of the kidney, stomach, cervix and nose and myeloid leukemia are also causally related to tobacco consumption[15]. Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades. On stopping smoking, the increase in risk of cancer induced by smoking rapidly ceases[16]. Benefit is evident within 5 years and is progressively more marked with the passage of time.

Smoking also causes many other diseases, most notably chronic obstruction pulmonary disease (commonly called chronic bronchitis) and an increased risk of both heart disease and stroke. The death rate of long-term cigarette smokers in middle age (from 35 to 69 years of age) is three times that of life-long non-smokers and approximately half of regular cigarette smokers, who started smoking early in life, eventually die because of their habit[17]. Half the deaths take place in middle age when the smokers lose approximately 20–25 year of life expectancy compared to non-smokers; the rest occur later in life when the loss of expectation of life is 7–8 years. There is, however, now clear evidence that stopping smoking before cancer or some other serious disease develops avoids most of the later risk of death from tobacco, even if cessation of smoking occurs in middle age[18]. While the rate at which young people start to smoke will be a major determinant of ill-health and mortality in the second half of this century, it is the extent to which current smokers give up the habit that will determine the mortality in the next few decades and which requires the urgent attention of public health authorities throughout Europe.

Tobacco smoke released to the environment by smokers, commonly referred to as environmental tobacco smoke (ETS) and which may be said to give rise to enforced 'passive smoking', has several deleterious effects on people who inhale it[15,19]. It causes a small increase in the risk of lung cancer and also some increase in the risk of heart disease and respiratory disease and is particularly harmful to small children. Smoking during pregnancy increases the risk of stillbirth, diminishes the infant's birth weight, and impairs the child's subsequent mental and physical development while smoking by either parent after the child's birth, increases the child's risk of respiratory tract infection, severe asthma, and sudden death.

Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke in inhaled and both cigar and pipe smoker cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx, and esophagus. There is strong scientific evidence that smokeless tobacco, whether sucked, chewed or inhaled, is associated with an increased risk of cancer.

Worldwide, it is estimated that smoking killed four million people each year: in the 1990s and that altogether some 60 million deaths were caused by tobacco in the second half of the Twentieth century. In most countries, the worst consequences of the "Tobacco Epidemic" are yet to emerge, particularly among women in developed countries and in the populations of developing countries, as, by the time the young smokers of today reach middle or old age, there will be approximately ten million deaths each year from tobacco (three million in the developed, seven million in the developing countries). If the current prevalence of smoking persists, approximately 500 million of the world's population today can expect to be killed by tobacco, 250 million in middle age.

The situation in women worldwide is alarming with the number of women smokers climbing and with the incidence and mortality of lung cancer in many countries now increasing rapidly. For example, while lung cancer mortality rates (a good surrogate marker for smoking trends and prevalence) have generally been falling in men in the European Union, there have been notable and continuing increases in lung cancer death rates in women[20].

In the past, it may have been felt that women have a different reaction to tobacco than men due to the wide disparity between tobacco-cancer rates in men and women. However, the effect on cancer rates only manifests itself beginning 20 years after the exposure to tobacco smoke first commences. Thus, there is a period of greater than 20 years, probably 30 or even 40 years, when the effects of smoking will not make their full impression on national cancer mortality rates. Therefore, when looking around and seeing a large proportion of smokers in women and particularly young

women, and no real impression on the rates of lung cancer, it is important to bear in mind that the real effect of the current tobacco smoking habits in younger women will not manifest themselves into cancer rates for at least 30 or 40 years. The current low levels of lung cancer and many other smoking-related cancers are falsely reassuring: women are not immune to the adverse health consequences of tobacco smoking as future cancer rates will clearly reflect. There are three important points. Firstly, men appear to have heeded the health education messages regarding tobacco smoking earlier than women. Secondly, there are indications that in several countries lung cancer rates in women will continue to increase for the foreseeable future and overtake breast cancer mortality[20]. Thirdly, the recent increase in smoking in younger women in several countries has not yet manifested itself as a lung cancer hazard although, based on current knowledge and past experience, this will come about. Obviously, the problem of tobacco smoking in women is a public health priority.

The great majority of lung cancer and the other diseases associated with tobacco smoking are avoidable[21]. It is a clear public health priority that women should be specifically targeted in Tobacco Control programs to reduce the smoking prevalence by reducing the number of young girls who take up the habit and by encouraging successful smoking cessation activities among adult women smokers.

Obesity and Physical Activity

Obesity is an established and major cause of morbidity and mortality[22]. It is the largest risk factor for chronic disease in Western countries after smoking, increasing in particular the risk for diabetes, cardiovascular disease and cancer[23]. Most countries in Europe have seen the prevalence of obesity (defined as a body mass index, BMI, of $\geqslant$30 kg/m^2) rapidly increase over the years. The prevalence can range from less than 10% in France to about 20% in the UK and Germany and higher in some Central European countries (>30%). It is associated with an increased risk of cancer at several sites and the evidence is clear for cancer of the colon, breast (post-menopausal), endometrium, kidney and esophagus (adenocarcinoma)[23–27]. There is still an excess risk after allowing for several factors such as physical activity. Overweight (BMI of 25–29 kg/m^2) is similarly associated with these cancers though the effect on risk will be less.

The risk of colon cancer increases approximately linearly with increasing BMI between 23 and 30 kg/m^2. Compared to having a BMI of <23 kg/m^2 there is about a 50–100% increase in risk in people with a BMI $\geqslant$30 kg/m^2. The association appears to be greater in men than in women. For example, in the *American Cancer Society* cohort study of about 1.2 million people, the increase in risk for colon cancer in those with a BMI of $\geqslant$30 kg/m^2 was 75% in men and 25% in women compared to those with a BMI of <25 kg/m^2. The evidence also suggests that the risk does not depend on whether the person had been overweight in early adulthood or later in life[25].

Over 100 studies have consistently shown a modest increased risk of breast cancer in postmenopausal women with a high body weight. On average, epidemiological studies have shown an increase in breast cancer risk above a BMI of 24 kg/m^2. A pooled analysis of 8 cohort studies[26] of about 340,000 women showed an increase in risk of 30% in women with a BMI $\geqslant$28 kg/m^2 compared to those with a BMI of <21 kg/m. Factors that have been shown to attenuate the association between obesity and breast cancer include family history (heavier women with a family history have a higher risk than similar women without a family history) and the use of hormone replacement therapy (the risk of breast cancer associated with obesity is greater in women who had never used HRT). In contrast, among premenopausal women obesity is not associated with an increase in risk.

There is consistent evidence that being overweight is associated with increased risk for endometrial cancer[23]. Women with a BMI of >25 kg/m^2 have a two- to three-fold increase in risk. Although limited, the evidence suggests that the risk is similar in pre- and post-menopausal women. There is evidence that the risk is greater for upper-body obesity.

The association between kidney (renal cell) cancer and BMI is also well established and is independent of blood pressure. Individuals with a BMI of $\geqslant$30 kg/m^2 have a two- to three-fold increase in risk compared to those below 25 kg/m^2. The effect is similar in men and women. There is a similarly strong association between being overweight and adenocarcinoma of the lower esophagus and the gastric cardia; about two-fold increase in risk in individuals with a BMI of >25 kg/m^2. A modest association has been reported in a pooled analysis of BMI and thyroid cancer (the increase in risk in those in the highest third of BMI was 20% in women and 50% in men)[27]. The evidence on obesity and gallbladder cancer is limited but there is a suggestion of almost a two-fold increase in risk, especially in women[28].

In Western Europe, it has been estimated that being overweight or obese accounts for approximately 11% of

all colon cancers, 9% of breast cancers, 39% of endometrial cancers, 37% of esophageal adenocarcinomas, 25% of renal cell cancer and 24% of gallbladder cancer.[29]

Physical activity

Many studies have examined the relationship between physical activity and the risk of developing cancer[23]. There is consistent evidence that some form of regular physical activity is associated with a reduction in the risk of colon cancer. There is also a suggestion of a risk reduction in relation to cancer of the breast, endometrium and prostate. The protective effect of physical activity on cancer risk improves with increasing levels of activity – the more the better – though such a recommendation should be moderated in individuals with cardiovascular disease. Regular physical activity that involves some exertion may be needed to maintain a healthy body weight, particularly for people with sedentary lifestyles. This could involve half an hour per day three times per week. More vigorous activity several times per week may give some additional benefits regarding cancer prevention.

For some cancers, the preventive effect of regular physical activity seems to act independently of weight control. The prevention of weight gain and obesity and the promotion of exercise ideally should begin early in life. However, the benefits can also be gained later in life if a healthy lifestyle is adopted. It is desirable to maintain a BMI in the range of 18.5 to 25 kg/m^2 and people who are already overweight or obese should aim to reduce their BMI to below 25 kg/m^2. A lifestyle that incorporates a healthy diet, exercise and weight control is beneficial to the individual not only with regards to cancer but also other diseases.

Diet and Nutrition

Diet and nutritional factors commenced to be the focus of serious attention in the etiology of cancer from the 1940s onwards. Initially dealing with the effect of feeding specific diets to animals receiving chemical carcinogens, research turned to the potential of associations with human cancer risk. Initially this was conducted through international comparisons of estimated national per capita food intake data with cancer mortality rates. It was consistently found that there were very strong correlations in these data, particularly with dietary fat intake and breast cancer. As dietary assessment methods became better, and certain methodological difficulties were identified and overcome, the science of *Nutritional Epidemiology* emerged[30].

Doll and Peto[8] estimated that somewhere between 10% and 70% of all cancer deaths were associated with dietary and nutritional practices, with the best estimate around 30%. In 1983, the *United States Academy of Science* concluded that after tobacco smoking, diet and nutrition was the single most important cause of cancer[31]. Since then, the epidemiological search has been to improve knowledge of the exact relationships between food and nutrition and cancer risk and to identify associations with particular components of diet and determine the best intervention strategy.

Initially much attention focused on intake of fat in the diet, particularly from animal sources. Although the results from ecological studies and data from animal experiments were very strong regarding this association[32], findings from retrospective and prospective epidemiological studies have generally been null particularly regarding the association with the breast cancer and colorectal cancer[33].

A number of epidemiological studies have indicated a protective effect of higher intakes of vegetables and fruit on the risk of a wide variety of cancers, in particular esophagus, stomach, colon, rectum and pancreas[34]. A higher consumption of vegetables and fruits has been associated with a reduced risk of cancer at various sites in several studies from Europe, mostly using a case-control design. The relation is however less consistent in data of several cohort studies from North America. If any, the association was apparently most marked for epithelial cancers, in particular those of the alimentary and respiratory tract, although such an association is weak to non-existent for hormone-related cancers.

Cereals with high fiber content and whole-grain cereals have been associated with lower risk of colorectal cancer and other digestive tract in a few European studies. However, several large cohort and randomized intervention studies have not supported this association. The EPIC study[35], examined this association in 519,978 individuals aged 25–70 years, recruited from ten European countries. Follow-up consisted of 1,939,011 person-years, and data for 1065 reported cases of colorectal cancer were included in the analysis. Dietary fiber in foods was inversely related to incidence of large bowel cancer (adjusted relative risk 0.75 [95% CI 0.59–0.95] for the highest versus lowest quintile of intake), the protective effect being greatest for the left side of the colon, and least for the rectum. After calibration with more detailed dietary data, the adjusted relative risk for the highest versus lowest quintile of fiber from food intake was 0.58 (0.41–0.85). No food source of fiber was significantly more protective than others, and non-food supplement sources of fiber were not investigated.

The authors concluded that in populations with low average intake of dietary fiber, an approximate doubling of total fiber intake from foods could reduce the risk of colorectal cancer by 40%. The confusing nature of this association between fiber intake and colorectal cancer risk is highlighted by the simultaneous publication of two studies, one of which confirmed this finding[35] and another, which reported no association[36].

Lower rates of many forms of cancer reported in southern European regions, like in Southern Europe, have been attributed to a diet lower in fats from animal sources, and meats, and higher in fish, olive oil, vegetables and fruits, grains, and moderate alcohol consumption[37]. While a link has been suggested with the (so-called) Mediterranean diet, this has not yet been proved convincingly, although encouraging findings have emerged from the recent report of a prospective study conducted in Greece[38]. A population-based, prospective investigation was conducted involving 22,043 adults in Greece who completed an extensive, validated, food-frequency questionnaire at base line. Adherence to the traditional Mediterranean diet was assessed by a 10-point Mediterranean-diet scale that incorporated the salient characteristics of this diet (range of scores, 0 to 9, with higher scores indicating greater adherence). During a median of 44 months of follow-up, there were 275 deaths. A higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality (adjusted hazard ratio for death associated with a two-point increment in the Mediterranean-diet score, 0.75 [95% CI 0.64–0.87]). An inverse association with greater adherence to this diet was evident for both death due to coronary heart disease (adjusted hazard ratio, 0.67 [95% CI 0.47–0.94]) and death due to cancer (adjusted hazard ratio, 0.76 [95% CI 0.59–0.98]). Greater adherence to the traditional Mediterranean diet appeared to be associated with a significant reduction in total mortality although associations between individual food groups contributing to the Mediterranean-diet score and total mortality were generally not significant[38].

The association with reduced risk of cancer exists for a wide variety of vegetables and fruits. There also exists increasing evidence that consumption of higher levels is also beneficial for other chronic diseases. Vegetables and fruits contain a large number of potentially anticarcinogenic agents, with complementary and overlapping mechanisms of action. However, the exact molecule(s) in vegetables and fruits which confers this protection is unknown and the exact mechanism of action is unknown. Insight into the mechanisms of action is only incomplete, but this is not required for public health recommendations. It is in any case not possible to recommend dietary supplementation with vitamins and minerals to reduce cancer risk based on the evidence currently available.

Nonetheless, it is difficult to be precise about the advisable quantity of fruits and vegetables and it is difficult to imagine the successful implementation of a randomized trial of increased consumption of fruits and vegetables. The best available evidence comes from *observational* studies and the search continues for the molecule(s) in fruits and vegetables responsible for the apparent protection.

Until recently, the evidence relating to breast cancer had been very weak but there has been an important development. Using the data collected in the prospective study of United States Nurses, Hunter et al.[39] showed an apparent protective effect of an index of vitamin A intake on breast cancer risk which had significant dose-response. Furthermore, there was a demonstrable effect of protection offered by use of vitamin A supplements in the fifth of women in the study who had the lowest intake levels of vitamin A. This issue is not yet resolved and the possibility remains that there may be some protection against breast cancer offered by increased intake of foods rich in vitamin A. A recent meta-analysis of 45 published studies of vegetables and fruits intake and breast cancer risk demonstrated a clear protective effect of high vegetable consumption compared to low consumption[40].

A clearer picture of the associations between dietary factors and cancer risk is currently being hampered by difficulties surrounding the assessment of dietary intakes. For example, pooled analyses of cohort studies show no relation between fat intake and breast-cancer risk. However, food-frequency questionnaire (FFQ) methods used in these studies are prone to measurement error. In the United Kingdom, diet was assessed with a food-frequency questionnaire and a detailed 7-day food diary in 13,070 women between 1993 and 1997. The authors compared 168 breast-cancer cases incident by 2000 with four matched controls. Risk of breast cancer was associated with saturated-fat intake measured with the food diary (hazard ratio 1.22 [95% CI 1.06–1.40], $p = 0.005$, per quintile increase in energy-adjusted fat intake), but not with saturated fat measured with the food-frequency questionnaire (1.10 [0.94–1.29], $p = 0.23$). The authors concluded that dietary measurement error might explain the absence of a significant association between dietary fat and breast-cancer risk in cohort studies[41].

The overall evidence from all types of studies suggests that increased consumption of vegetables and fruits

can lead to a reduction of the risk of several forms of cancer which are common in men and women. Fruits and vegetables should be taken with each meal whenever possible, and systematically replace snacks in between meals. In line with World Health Organisation (WHO) and United States recommendations, 'Five-a-day' (minimum 400 g/day, i.e. 2 pieces of fruit and 200 g of vegetables) is advocated, which could lead to a reduction in cancer risk. Particular attention regarding changing nutritional practices needs to be paid to the countries of central and Eastern Europe, where rapid changes in dietary patterns have been shown to have had a rapid, and positive influence, on death rates from chronic disease.[42]

Alcohol Consumption

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and larynx and of squamous cell carcinoma of the esophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident[43].

Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared to never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. Indeed, in the case of total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell esophageal cancers in European countries would have been extremely low[44].

A likely carcinogenic mechanism of alcohol is by facilitating the carcinogenic effect of tobacco and possibly of other carcinogens to which the upper digestive and respiratory tract are exposed, particularly those of dietary origin. A diet poor in fruits and vegetables, typical of heavy drinkers, is also likely to play an important role. There does not seem to be a different effect of beer, wine or spirits on cancer risk at these sites; rather the total amount of ethanol ingested appears to be the key factor in determining the increase in risk. Only few studies have analyzed the relation between stopping alcohol drinking and the risk of cancers of the upper respiratory and digestive tract. There is clear evidence that the risk of esophageal cancer is reduced by 60% ten years or more after drinking cessation.[44] The pattern of risk is less clear for oral and laryngeal cancers. Stopping (or reducing) alcohol drinking, particularly in association with smoking cessation, represents a priority for preventing esophageal cancer.

Alcohol drinking is also strongly associated with the risk of primary liver cancer; the mechanism however might be mainly or solely via the development of liver cirrhosis, implying that light or moderate drinking may have limited influence on liver cancer risk. Moreover, there is some evidence suggesting that heavy alcohol consumption is particularly strongly associated with liver cancer among smokers and among people chronically infected with Hepatitis C virus.

An increased risk of colorectal cancer associated with alcohol drinking has been observed in many cohort and case-control studies[45], which seems to be linearly correlated with the amount of alcohol consumed and independent from the type of beverage.

An increased risk of breast cancer has been consistently reported in epidemiological studies conducted in different populations[46]. Although not strong (increase risk in the order of 10% for each 10 g/day increase in alcohol intake, possibly reaching a plateau at the highest levels of intake), the association is of great importance because of the apparent lack of a threshold, the large number of women drinking a small amount of alcohol and the high incidence of the disease. Indeed, more cases of breast cancer than of any other cancer are attributable to alcohol drinking among European women (Table 10). It has been suggested that alcohol acts on hormonal factors involved in breast carcinogenesis, but the evidence is currently inadequate to identify a specific mechanism.

Besides increasing cancer risk, alcohol drinking entails complex health consequences. There is strong evidence for a J-shaped pattern of risk of total mortality and cardiovascular disease according to increasing alcohol consumption[47]. This classic pattern is one of decreased risk in light drinkers compared to non-drinkers and then an increasing risk as alcohol consumption increases. In addition, alcohol drinking increases the risk of injuries in many types of motor vehicle, leisure and occupational injuries (e.g. driving, swimming, manual working) and accident mortality rates are influenced by per capita alcohol consumption across Europe[48]. Moreover, alcohol during pregnancy has a detrimental effect on the development of the fetus and its CNS, often resulting in malformations, behavioral disorders and cognitive deficits in the postnatal period.

For these reasons, the task of fixing a threshold on daily alcohol intake below which the increased risk of

Table 10
Estimated number and proportion of cancer cases attributable to alcohol consumption in women in the European Union (1995)

Cancer	Women	
	N	%
Oral cavity and pharynx	2700	29
Esophagus	2100	34
Liver	500	25
Larynx	1200	13
Breast	6000	3

Sources: All information taken from Pisani P. Avoidable Cancer in Europe: Estimating Etiologic Fractions. Final Report to the European Commission, Contract No. 96–200504. Lyon, IARC, 2000. The exception is breast cancer which was calculated based on a relative risk of 1.1 and prevalence of exposure of 30%.

cancer and other diseases is offset by a reduced risk of cardiovascular diseases is not simple. Factors such as age, physiological conditions and dietary intake certainly modify any such threshold: in particular, the beneficial effects on cardiovascular diseases appear only at middle age.

There is evidence showing that a daily alcohol intake as low as 10 g/day (that is, approximately, one can of beer, one glass of wine or one shot of spirit) is associated with some increase in breast cancer risk relative to non drinkers, while the intake associated with a significant risk of cancer at other sites (such as cancers of the upper digestive and respiratory tracts, liver or colorectum) is probably somewhat higher (approximately 20–30 g/day).

All the above points should be considered to give sensible advice regarding individual recommended limits of alcohol consumption. The limit should not exceed between 20 g of ethanol per day (i.e. approximately two drinks of either beer, wine or spirit each day) and it should be as low as 10 g per day for women.

Sun Exposure

Skin cancer is predominantly, but not exclusively, a disease of white-skinned people. Its incidence is greatest where fair-skinned peoples live at increased exposure to ultraviolet light, such as in Australia. The main environmental cause of skin cancers is sun exposure, and the ultraviolet light is deemed to represent the component of the solar spectrum involved in skin cancer occurrence.

The type of sun exposure which causes skin cancer however appears to differ in the three main types. Squamous cell carcinoma shows the clearest relationship between cumulative sun exposure. This form of skin cancer is therefore most common in outdoor workers. The recipients of transplanted organs are particularly at risk of these tumors as a result of the combined effects of the unchecked growth of human papilloma virus in their skin due to immuno-suppression, and exposure to the sun[49]. Basal cell carcinoma is the commonest type of skin cancer but it is the least serious as it is a local disease only. This form of skin cancer appears to share an etiological relationship to sun exposure with melanoma[50].

The risk of cutaneous melanoma appears to be related to intermittent sun exposure[51,52]. Examples of intermittent sun exposure are sunbathing activities and outdoor sport activities. Also, a history of sunburn has repeatedly been described as a risk factor for melanoma, which again is associated with intermittent sun exposure.

The incidence of melanoma doubled in Europe between the 1960s and the 1990s and this is attributed to increased intense sun exposure, which has taken place this century. The incidence of squamous cell and of basal cell cancers has also increased in all European countries. Although much less life threatening than melanoma, these tumors represent 95% of all skin cancers, and their treatment conduct to considerable costs for individuals and social security systems.

It is clear that individuals should moderate their sun exposure: to reduce their total lifetime exposure, and in particular to avoid extremes of sun exposure and sunburn in particular. All individuals however are not equally susceptible to skin cancer. The fairest are more susceptible, particularly those with red hair (but not exclusively), freckles and a tendency to burn in the sun.

The strongest phenotypic risk factor for melanoma however is the presence of large numbers of moles or melanocytic naevi and twin study evidence is strong that the major determinant of naevus number is genetic with an added contribution from sun exposure[53,54].

These naevi may be normal in appearance but are also usually accompanied by so-called atypical moles: moles which are larger than 5 mm in diameter with variable color within and an irregular shape[55]. The phenotype is described as the atypical mole syndrome phenotype (AMS). The AMS is present in something like 2% of the North European population and is associated with approximately a ten times increased risk of melanoma. Advice about sun protection is therefore particularly of importance to this sector of the population. Some patients with the AMS report a family history and overall a strong (3 or more cases) family history is the strongest predictor of risk. These families should avoid the sun and should be referred up to dermatologists for counselling.

The best protection from the summer sun is to stay out of it and case is needed in order to allow safer enjoyment of the outdoors. Keeping out of the sun between 11 am and 3 pm is effective as ultraviolet (UV) exposure is greatest at this time. Therefore scheduling outdoor activities for other times is important, particularly for children. Using shade is allied to this and clothing remains the second most important measure. Close weave heavy cotton affords good protection although the clothing industry increasingly is developing UV protective clothes with high sun protection properties which are very valuable particularly where it is difficult to keep out of the sun.

Sunscreens are useful for protection against sunburns of skin sites such as the face and the ears. Sunscreen may protect against squamous cell carcinoma but there is currently inadequate evidence for a preventive effect against basal cell carcinoma and melanoma[56,57]. However it is extremely important when using sunscreen to avoid prolongation of the duration of sun exposure that may be responsible for an increased risk of melanoma[58]. In addition, sunbed use is also discouraged, as exposure to these devices resembles to the type of sun exposure mostly associated with melanoma occurrence.

Occupational and Environmental Exposures

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to significant reductions in cancer occurrence.[59] Historically, these occupational carcinogens have particularly affected men rather than women and, therefore, of the estimated 5% of cancers attributable to the occupational environment.[60] A much smaller proportion is attributable in women. This proportion depends on the variable prevalence of the exposures by geographical areas, socioeconomic status and periods of time, as well as on the concurrent prevalence of other dominant cancer causing factors particularly tobacco smoking.

Environmental exposures usually refer to exposures of the general population that cannot be directly controlled by the individual. They include air-pollution, drinking water contaminants, passive smoking, radon in buildings, exposure to solar radiation and to low frequency electromagnetic fields, food contaminants such as pesticide residues, dioxins or environmental estrogens, chemicals from industrial emissions, and other. Exposure may be widespread as is the case for air pollution or could be restricted, as would be the case of populations living in the vicinity of a contaminating industry. These exposures have been associated with a variety of neoplasms including cancers of the lung, urinary bladder, leukemia and skin. Air pollutants such as fine particles, have been associated in several studies with a small increased risk for lung cancer even at current low-level urban exposure levels. Agents in the general environment to which a large number of subjects are exposed for long periods, such as passive smoking or air-pollution, although increasing only modestly the relative risk for certain cancers may be at the origin of a sizeable number of cases, running into several thousands yearly in the European Union.

Ionizing radiation at **high** doses causes cancer in humans: only a few cancer types have never been related to ionizing radiation. This has been known for decades, and excellent summaries of the scientific literature are available. The *International Agency for Research on Cancer* (IARC) recently classified X-rays, γ-rays and neutrons as carcinogenic to humans (Group 1).[61,62] This is irrespective of the different patterns of energy release and penetrating power of the different types of ionizing radiation. Energy at high levels may lead to cellular damage to the DNA followed by cell killing, whereas at lower doses it may lead to mutations increasing the risk of cancer. The *International Commission on Radiological Protection* (ICRP)[63] issues recommendations for radiological protection based on the existing scientific literature.

High-dose ionizing radiation is used in medicine to treat cancer and much of our evidence on the effects of ionizing radiation on humans is derived from such uses, and from the atomic bomb survivors at Hiroshima and Nagasaki. The main source of radiation to the human population comes from the natural background, both terrestrial and cosmic, whilst the man made sources, such as from atmospheric nuclear testing, nuclear accidents

Table 11
Source of ionizing radiation to man

Source	Worldwide average annual effective dose[a]
Natural background	2.4
Diagnostic medical examinations	0.3
Atmospheric nuclear testing	0.005
Chernobyl accident	0.002
Nuclear power production	0.001

[a]Average radiation doses at year 2000 from natural and man-made sources of radiation, expressed in millisievert (mSv).
Source: UNSCEAR www.unscear.org/press_releases.htm 49th session, Vienna 2–11 May 2000.

(e.g. Chernobyl) and nuclear power production cause the most public concern (Table 11).

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates the population risk of dying from cancer after an acute dose of 1000 mSv is about 9% for men and 13% for women. The estimates could be reduced by 50% for chronic exposures. The annual worldwide average annual effective dose is 2.4 mSv. The lifetime exposure of the population to all sources of ionizing radiation was by the NRPB estimated to account for 1% of all fatal cancers in the UK. (http://www.nrpb.org/radiation topics/risks/cancer risk.htm – 22 November 2002) Only 1% of this risk is ascribed to the small doses from man-made radiation.

Diagnostic radiation is of concern for the population groups undergoing examinations, be it screening of healthy individuals with mammography or CT scans for lung cancer or when there is a suspicion of thyroid disease. Screening with low-dose CT for lung cancer is reported to give an effective dose of between 0.2 and 1 mSv. Using the risk factor of 5% per 1 Sv (ICRP 60), this would imply 1–5 radiation-induced fatal cancers per 100,000 examinations. Mammography screening for breast cancer typically gives an absorbed average glandular dose of 3 mGy. It has been estimated in Sweden that among women aged 50–69, with a reduction in breast cancer mortality due to a mammographic screening program of 25%, that 560 deaths from breast cancer would be avoided. It is estimated that the effect of the radiation would be to induce between 1 and 5 fatal breast cancers per 100,000 examinations. Although the collective dose from diagnostics to the population is small relative to natural radiation, benefit analyses should be performed to avoid unnecessary exposure.

The major concern regarding medical use of ionizing radiation has been the possibility that thyroid examinations or treatments using radioiodine causes thyroid cancer. The annual number of thyroid examinations using radioiodine is currently 5 per 1000 individuals in the western world. Patients treated with I_{131} for hyperthyroidism are almost entirely adults and no increased risk of thyroid cancer is seen among these patients.[64] It is also likely that the doses, ranging from 100 to 300 Gy, received by the thyroid gland induce cell killing instead of carcinogenic transformation.

Radon and Cancer

There is conclusive evidence from studies of underground miners occupationally exposed to high concentrations of radon in air that radon is a cause of lung cancer.[65] Extrapolation from the miners' studies to the likely effects of environmental exposure to radon suggests that radon should be the second most important cause of lung cancer in the general population after cigarette smoking, and that the majority of radon-induced lung cancers are in those who smoke cigarettes or who have smoked them in the past.[66] Direct studies of the risk of lung cancer from residential radon exposure are consistent with these conclusions. The studies of underground miners and also some direct studies suggest that high concentrations of radon in air do not cause a material risk of death from cancers other than lung cancer. When a new house or other building is being constructed, it is usually possible, for a minimal cost, to ensure that the radon concentration inside the building will be very low. For existing buildings it is also usually possible at some cost to reduce the radon concentrations. In terms of risk reduction, such measures will have their biggest effect on smoking inhabitants.

The overwhelming evidence does not point to a significant adverse health effect of exposure to cosmic radiation in terms of cancer[67] and the present regulation of aircrew as radiation workers sufficiently regulates the occupational exposure.[68] Only few passengers will ever

accumulate radiation doses from cosmic radiation in the same magnitude as the staff and hence no particular precautions needs to be taken.

There does not appear to have been a general increase in rates of adult cancers around nuclear installations. Some – but not all – studies have indicated increased rates of childhood cancers and particularly childhood leukemia.[69] The evidence for such increases has tended to be strongest in the vicinity of the nuclear reprocessing plants; in particular, Sellafield and Dounreay in the UK and, to a lesser extent, La Hague in France. Interpretation of these studies has been hindered in part by small numbers of cases and by the ecological (correlation) study design used in many instances. Assessments of radiation doses to those living near these installations do not suggest that the raised childhood leukemia risks can be explained on the basis of radioactive discharges. At present, specific actions are not indicated over and above existing guidelines on radiation exposures to members of the public.

Power lines produce extremely low frequency (ELF) electromagnetic fields in range of 50 Hz to 60 Hz. Electric fields do not reach people inside the houses but magnetic fields go through most materials and cause an additional exposure higher than the typical background field (about 0.1 μT) up to a distance roughly 50 meters from the power line, depending on the voltage and wire configuration. Health effects on humans related to this non-ionizing type of radiation have been investigated in epidemiological studies for over two decades.

It appears on the basis of studies with large numbers of cancer cases that there is no excess risk of cancer among adults living close to power lines, but the results of occupational studies are suggestive of an association with some cancers including adult leukemia. IARC[70] classified it its evaluation (monographs volume 80, IARC 2002) ELF magnetic fields as possibly carcinogenic to humans (Group 2b), while ELF electric fields were considered not to be classifiable as to their carcinogenicity to humans (Group 3). This evaluation only considers the likelihood of an association but does not take into account the magnitude of the possible risk on individual nor the population attributable risk. The results of epidemiological studies suggest that appreciable magnetic field effects, if any, are concentrated among relatively high and uncommon exposures.

The use of cellular phones and possible adverse health effects related to the use, attract much attention. Reports on brain tumor excesses occurring among phone users, case stories in the press and reports on thermal as well as magnetic effects on exposed tissue hypothesized to stimulate tumor growth, combined with the explosion in subscribers to cellular phones, raise public concern. The radiation from the cellular phones is characterized as non-ionizing alongside radar, microwave ovens and electrical wiring configuration. The radio frequency signals emitted from the devices range between 450 and 2200 MHz, i.e. in the microwave region of the electromagnetic spectrum. Recently a comprehensive review on the epidemiological literature was carried out by Boice and McLaughlin[71] and published by the Swedish Radiation Protection Authority. They conclude after review of 9 major studies, two cohort studies on cancer, three hospital based case-control studies, one incidence population based case-control study and two prevalence-based case-control studies, that no significant association is present for brain tumors and use of cellular phones, irrespective of duration of use, type of phone (digital or analogue), tumor morphology or laterality. The follow-up, however, is short, and even if relative risks are unlikely to exceed 1.3 it is important to monitor this exposure to exclude the possibility of any long-term effects. On the other hand, no biological mechanism supports a causal relation and there is no evidence of adverse effects from laboratory animals. However, use of mobile telephones while driving certainly increases the risk of accident.[72]

PUBLIC HEALTH PROGRAMS

Much effort has gone into cancer screening and the development of methods of finding cancers at an earlier stage in their development and increasing prospects for cure. It is possible to make recommendations based on the available evidence.

Cervix Cancer Screening

In many low- and medium-resource countries, the uterine cervix is one of the most prevalent sites for cancer, frequently comprising about 25% of all female cancers. In industrialized populations, the disease is less common. In eastern and central European populations, the annual age-adjusted (using the World Standard Population as referent) incidence rates for invasive disease are 15–25 per 100,000 women. In the Nordic countries, the annual incidence was 15–30 per 100,000 women before the start of large-scale mass screening programs.

The effectiveness of screening for cervical cancer has never been demonstrated in a randomized trial. There is, however, sufficient non-experimental evidence showing the efficacy of screening using a cervical smear (Pap) test

performed every 3–5 years. This is based on case-control and cohort studies and on time trends and geographical differences associated within screening. The largest of these is the collaborative study co-ordinated by the *International Agency for Research on Cancer* which showed that eradication of the disease is an unrealistic goal and that maximal protection after a negative smear is about 90%, which remains roughly the same during several years after the test[73]. This conclusion is in agreement with the results of studies on the natural history of the disease, which have shown that most pre-invasive lesions progress to frankly invasive cancer only over several years.

The effects are somewhat smaller at a population level. In some of the Nordic countries, the reduction was about 80% in women in the age groups exposed most intensively to screening. In the mid-1980s, after several years of organized screening, the overall incidence was 5–15 per 100,000 woman-years[74].

Cervix cancer screening should be offered to all women over 25 years[3]. There is limited evidence of benefit of screening in women over 60 though the likely yield of screening is low in women over age 60 since the incidence of high-grade cervical lesions declines after middle age. Screening this age group is associated with potential harms from false-positive results and subsequent invasive procedures. Stopping screening in older women is probably appropriate among women who have had 3 or more consecutive previous (recent) normal Pap smear results. Yield is also low after hysterectomy and there is scant evidence to suggest that screening produces improved health outcomes.

An organized program consists of several essential elements[75]. Defining the population to be screened is important. Personal invitation is the single most important means of attaining high attendance, especially when it is combined with effective information through the mass media. Free service has also been shown to improve attendance. Quality assurance of all steps of the process, monitoring and constant evaluation of the proportion of cancer detected, false positives and false negative readings, are mandatory[76]. Near maximal effectiveness is achieved by an organized program with high coverage, in which screening is initiated at the age of 25 and is repeated at three- or five-yearly intervals to the age of 60. Extension of this approach should be considered only if maximal coverage has been attained, the resources are available and the marginal cost-effectiveness of the recommended changes has been evaluated. *European Union Guidelines for Quality Control in Cervix Cancer Screening* have been developed and are widely followed in Europe[76].

Infection with certain strains of Human Papilloma Virus (HPV), generally acquired sexually, is the most important risk factor for cervical cancer[77]. With the use of (modern) HPV detection methods over 90% of squamous cell cervical cancer and 75–85% of high-grade CIN lesions have detectable HPV DNA. Given the implication of HPV infection in cervical cancer, detecting HPV could represent an appealing screening method[78]. A study of 2009 women having routine screening in England and Wales, showed that 44% of cervical intraepithelial neoplasia (CIN) lesions of grade 2/3 detected had negative cytology and were found only by HPV testing (for types 16, 18, 31 and 33): a further 22% were positive for HPV but demonstrated only borderline or mild cytological changes. However, 25% of CIN 2/3 lesions were not detected by the four HPV tests.

Routine HPV testing for cervical cancer screening is still a research topic at present as HPV infection is very common in women less than 30 years old, and what matters are those women over the age of 30 with a HPV infection that persists over a long period of time. HPV testing is still to be evaluated to find the role it could play in cervical cancer screening. It has the potential to become an important test in detecting cervix lesions in future[79] and should be a current research priority.

Mammographic Screening for Breast Cancer

Mammography can detect tumors at a clinically undetectable stage[80]. The results from the early-randomized trials of mammographic screening demonstrated the value of mammographic screening and led to the introduction of organized national programs of screening in several countries in 1986–8. Reports from seven trials involving over half a million women subsequently indicated a reduction in mortality from breast cancer of about 25% in women invited to be screened[81,82]. The reduction of mortality in those actually attending for screening is about one third[83].

There is now considerable evidence that breast cancer screening with mammography is effective at reducing mortality from breast cancer. An overview of the Swedish trials reported relative risks of death of 0.71 in the group randomized to and offer of screening with 95% confidence interval 0.57–0.89 for women aged 50–59 at entry. Results for women ages 60–69 were almost identical. When applied to a population a well-organized program with a good compliance should lead to a

reduction in breast cancer mortality of at least 20% in women aged over 50.

The value of screening women under 50 years is uncertain[84]. No trials having large enough statistical power to analyze these women separately. What recommendations should be made for mammographic screening of women aged between 40 and 49 is an important question that cannot now be answered; over 40% of the years of life lost due to breast cancer diagnosed before the age of 80 years are attributable to cases presenting symptomatically at ages 35–49 years, frequently an age of considerable social responsibility.

Swedish workers have recently conducted an overview of four of their trials[81]. The conclusions indicate that the benefit of breast screening, in terms of a reduction in breast cancer mortality of 21%, persists for a median time of 15.8 years. Additional to this overview, two Working Groups have been convened. A working group of the *International Agency for Cancer Research* (IARC)[83], which met in Lyon on 5–12 March 2002, which consisted of 24 experts from 11 countries. The quality of the seven trials was assessed and it was concluded that screening by mammography reduced mortality from breast cancer in women of 50–69 years of age. In women who participated in screening programs this was estimated at reduction 35%. For women of 40–49, evidence for a reduction in mortality was too limited to reach a conclusion. The evidence is insufficient to recommend performing routine breast self-examination as a method of screening.

Forty years of clinical trials, the contribution of hundreds of scientists and health workers and the dedication of hundreds of thousands of women to participate in studies lasting for decades has resulted in adequate evidence to support the efficacy of mammographic screening for breast cancer, which now allows its transfer to the arena of Public Health Care. Doctors and women should be assured that participation in organized screening programs with high quality control standards is of benefit, provided appropriate investigation and treatment is available. *European Guidelines for Quality Control in Mammographic Screening* have been developed and are widely employed throughout Europe[85].

Special efforts should be made to encourage screening among the more deprived members of communities. It is important not to overemphasise the benefit of screening, and to appreciate that mammographic screening is but one step in the total care of women with the disease. As had been shown from long-term established programs in United Kingdom, Sweden, Finland and the Netherlands, recognition of the importance of the multidisciplinary team in the assessment of mammographic abnormalities had spread into the symptomatic sector leading to the development of integrated multidisciplinary breast care centers. Staffed by dedicated surgeons, radiologists and pathologists working alongside breast care nurses, counselling and other support personnel, these centers offered the necessary care for women with breast cancer.

Colorectal Cancer Screening

The identification of a well-determined pre-malignant lesion, the adenomatous polyp[86], together with the good survival associated with early disease, make colorectal cancer an ideal candidate for screening. In the past quarter century, progress has been made in our ability to screen patients for colorectal cancer or its precursor state, using advances in imaging and diagnostic technology. Fecal occult blood guaiac test cards were first employed in the 1960s[87,88], the flexible sigmoidoscope was introduced in the mid-1970s to replace the rigid sigmoidoscope which had been first introduced in 1870, and colonoscopy has been available since 1970.

Randomized trials have examined annual or biennial screening with Fecal Occult Blood Testing (FOBT)[89–91] while there are only data available regarding sigmoidoscopy and colonoscopy from observational studies, and little yet from randomized trials. There is evidence from these randomized trials to support the use of FOBT with a reduction in colorectal cancer mortality of around 16% (95% CI 9–22%) from a meta-analysis [27% (95% CI 10–43%) reduction among those screened][92]. The proposed screening interval is 2 years, though it has been judged that yearly examinations are cost-effective.

Flexible sigmoidoscopy is an alternative or complementary method of screening whose efficacy has been consistently demonstrated in observational studies[93]. A large randomized trial is underway which should have results in 2005 or 2006. The higher sensitivity of colonoscopy over FOBT suggests that colonoscopy could be more effective[94,95].

Despite the accumulating evidence showing that screening for colorectal cancer is worthwhile, most citizens of developed countries have not been screened for colorectal cancer by any means. While this situation persists the chance is being missed to prevent about one quarter of the 138,000 colorectal cancer deaths which occur each year in the European Union. Special efforts are required against colorectal cancer which is now the most common malignant disease in the population of the European Union.

Vaccination against Human Papilloma Virus and Hepatitis B infection

About 16% of human cancers worldwide are currently attributable to persistent infections with viruses, bacteria or parasites[96]. In the European Union this fraction is about 10%, and it is chiefly accounted by four cancer sites or types, namely cancer of the cervix uteri, liver, stomach and some hemo-lymphopoietic tumors. Knowledge about the role of infectious agents in the etiology of several cancer types has rapidly expanded in the last 30 years, after major improvements were made in the detection of markers of chronic infection. Contrary to former beliefs, anti-bacterial and anti-viral treatments, as well as vaccination programs, represent an important tool against cancer.

Every year approximately 25,000 women in the EU develop cervical cancer. A dozen types of human papillomavirus (HPV) have been identified in 99% of biopsy specimens from cervical cancer worldwide and, in Europe, HPV 16 has been reported in 56% of over 3,000 cervical cancer specimens. Five HPV types (HPV 16, 18, 31, 33, 45) account for more than 85% of European cervical cancer specimens[97]. In control women, the prevalence of the indicated HPV types is several dozen-fold lower. There is no effective medical treatment against HPV, but very sensitive and specific tests for the detection of HPV DNA in cervical cells have become available. There is sufficient evidence for recommending HPV testing among women who show borderline or low-grade cytological abnormalities. Additionally, HPV testing improves the follow-up of women who have been treated for cervical intra-epithelial lesions (CIN) and, pending results of ongoing trials, may offer a more sensitive alternative to cytology in primary cervical cancer screening.

A prophylactic vaccine, based on late (L) 1 HPV 16 proteins, has been shown to be safe, highly immunogenic, and efficacious in preventing persistent HPV infections in a trial of 1523 HPV 16-negative young women in the United States[98]. A multivalent vaccine against the most common oncogenic HPV types may thus ultimately represent the most effective way to prevent cervical cancer worldwide alone or in combination with screening. Vaccination would benefit women who do not attend screening programs in the EU and, if combined to current screening programs, it would allow substantial savings (i.e., less frequent screening tests, fewer treatments, etc.).

Every year approximately 30,000 new cases of liver cancer are recorded in the European Union. Upward trends in incidence and mortality rates have been seen, in the last two decades, in men in France, Germany and Italy[99]. Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounts for the majority of liver cancer cases in Europe. In a large case-series of liver cancer from six European Liver Centers only 29% of 503 liver cancer patients had no marker of either HBV or HCV infection[100].

An effective vaccine against HBV has been available for 20 years now. Several countries in the European Union (e.g., Denmark, Finland, Ireland, the Netherlands, Sweden and the United Kingdom) do not perform routine vaccination against HBV in children, on account of low prevalence of HBV infection in the general population (http://www.who.int/), whereas other countries (e.g., Belgium, France, Germany) report coverage below 50%. There is scope for reconsidering national policies regarding universal vaccination against HBV since selective vaccination of high-risk groups rarely works and travelling and migration facilitate the mixing of high- and low-risk populations. Although infection with HBV in young adulthood (typically through sexual intercourse or contaminated needles) carries a much lower risk of chronic hepatitis and liver cancer than infection at birth or during childhood, it frequently induces acute hepatitis.

HCV represents an increasing problem in several areas of the EU (especially in Italy, Greece and Spain) and in some population groups, notably intra-venous drug users. A vaccine is not yet available however.

Infectious agents account for a substantial fraction of cancer in women. For the moment, priorities are the expansion of immunization programs against HBV and the inclusion of HPV testing in cervical cancer screening programs. Vaccines against cancer-causing infectious agents are, however, one of the most promising ways to prevent or even cure some important tumors. Because of the enormous cost of vaccine development, public-private partnerships (e.g., the Global Alliance for Vaccines and Immunization, GAVI[101] for developing countries) should be actively pursued in the EU, especially with respect to the development of vaccines against HCV and Hp.

Other Potential Actions which may alter Cancer Risk

There have been a number of additional strategies or actions proposed which could lead to a reduction in cancer incidence or mortality. However, the evidence is not so certain that any recommendation could be made

with a convincing probability of success in reducing cancer risk.

There have been several studies which have proposed chemopreventive actions of a variety of vitamins and minerals (beta-carotene, selenium, vitamin C etc). However, there is no convincing body of evidence yet available to support such actions[3].

In five randomized trials, dietary supplementation with wheat bran or other types of fiber did not affect the rate of recurrence of colorectal adenomas[102–106]. It appears from the results of these randomized trials that supplementation with fiber does not affect the risk of the recurrence of colorectal polyps. The evidence on a protective effect of fiber against colorectal cancer is purely observational and the use of fiber cannot be recommended to the general population at the present time. The evidence suggesting that calcium supplementation decreases risk of colorectal adenomas is not yet sufficient to recommend its use to the general population as a strategy to prevent colorectal cancer.

Despite some positive results obtained in studies in humans and coupled with biological plausibility[107], the efficacy of long-term NSAIDs prophylaxis against colorectal cancer, and other cancers, remains unproven. Recommendations regarding the use of NSAIDs for prevention of colorectal cancer, except probably the use of celecoxib or sulindac for control of the growth of colorectal adenomas among patients with FAP, appears to be premature at the present time.

Tamoxifen

Five trials have now reported on the use of tamoxifen and raloxifen for prevention of breast cancer[108–112]. Four trials compared 20 mg tamoxifen daily for at least five years with placebo[113]. One trial compared two doses of raloxifen (60 mg or 120 mg) with placebo. Cuzick et al.[113] report an overview of the main outcomes of these prevention trials and adjuvant trials in which tamoxifen treatment was at least 3 years with doses 20–40 mg. The combined data from tamoxifen prevention trials supported a reduction in breast cancer incidence by 38% (95% CI 28–46, $p < 0.001$). The adjuvant studies and the raloxifen trial showed greater reduction (46% [95% CI 29–63] and 64% [95% CI 44–78]). There was no effect for breast cancers negative for estrogen receptors, but ER-positive cancers were decreased by 48% [95% CI 36–58]. Rates of endometrial cancer were increased in all tamoxifen prevention trials (RR = 2.4, 95% CI 1.5–2.6). No increase has been seen with raloxifen. Venous thromboembolic events were increased in all tamoxifen studies and with raloxifen.

The evidence now clearly shows that tamoxifen can reduce the risk of ER-positive breast cancer. However, high rates of side effects do not permit to recommend the prophylactic use of tamoxifen in healthy women based on current evidence.

Oral Contraceptives (OC)

The main established evidence on the issue of Oral Contraceptive (OC) usage and cancer risk issue can be summarized[3] as supporting that here is a moderately increased risk for breast cancer among current, but not former OC users; OC use lowers the risk of endometrial and ovarian cancer, and the protection seems to persist after cessation of use; a reduced risk of colorectal cancer among OC users is possible, but this issue is still open to discussion; and OC are related to increased risk of cervical cancer and liver cancer, but the public health importance of these associations is small in developed countries.

OC have been used for 40 years, and the formulations have been modified repeatedly. It is therefore difficult to propose further modifications which may appear favorable on the risk of selected diseases without increasing the risk of other side effects.

Hormonal Replacement Therapy (HRT)

HRT has been reported to increase breast cancer risk and to be positively associated with ovarian cancer risk, and inversely to colorectal cancer risk.

Important information on cancer risk in users of combined estrogen and progestogen HRT comes for the Women's Health Initiative (WHI), a randomized primary prevention trial including 8,506 women aged 50 to 70 treated with combined HRT and 8,102 untreated women[114]. The combined treatment group was closed in May 2002, whereas an additional estrogen only group is still ongoing (as of November 2002). With respect to breast cancer, no difference in risk was evident for the first four years after starting treatment, but an excess risk was evident thereafter. At the 7-year follow-up, 166 breast cancer cases were registered in the treated group versus 124 in the placebo group, corresponding to a RR of 1.24 (95% CI 1.03–1.66). Data from two other smaller randomized studies are available: one (HERS) with combined estrogen/progestogen therapy, and one (WEST) with estrogen only. In a combined analysis of the three randomized trials, 205 cases of breast cancer were registered in the treated groups, versus 154 in the placebo, corresponding to an overall RR of 1.27. Since, however, this estimate is heavily weighted by the WHI study, the quantitative role of estrogen only HRT on breast cancer risk cannot be conclusively documented.

Data on endometrial cancer are available from the WHI and the HERS[115] study, both based on combined therapy. Overall, 24 cases were observed in the combined HRT groups versus 30 in the placebo ones, corresponding to a pooled RR of 0.76.

With reference to colorectal cancer, the combined analysis of the WHI and HERS studies included 56 cases in the HRT treated group and 83 cases in the placebo group (RR = 0.64).

Thus, with reference HRT and cancer risk, the recent findings of randomized trials are in broad agreement with those of observational (cohort and case-control) studies, and provide therefore strong evidence that: (1) combined estrogen/progestogen HRT is associated with a moderate excess risk of breast cancer, which becomes evident after a few years of use. Such an increased risk appears to be restricted to current users; (2) the pattern of risk in relation to HRT use appears similar for ovarian cancer, although data remain inadequate; (3) unopposed estrogens are strongly related, but combined HRT is not associated to a material excess risk of endometrial cancer; and (4) HRT may have a favorable effect on colorectal cancer risk, although the relation with duration and other time-related factors remains unclear.

Considering also the apparently adverse effects of HRT on cardiovascular diseases, HRT should not be recommended for disease prevention. HRT remains indicated for short-term symptoms relief, while other treatments should be considered for osteoporosis.

SUMMARY AND CONCLUSIONS

The increasing and ageing female population worldwide will result in increases in the absolute numbers of incident cases of cancers world wide. In the absence of major advances in the outcome of therapy, this will result in an increasing number of cancer deaths in women.

The majority of deaths from cancer can now be avoided by a combination of primary prevention and screening. Everyone has lifestyle choices to make, and it is clear that some of them could readily lead to reductions in the risk of chronic diseases including cancer.

Currently available knowledge indicates that the issues laid out above are crucial to forming, and also altering, the cancer risk to an individual woman. Cancer Control is within our grasp but we need to make the effort to bring it about.

ACKNOWLEDGEMENTS

This work was conducted within the framework of support from the *Associazione Italiana per la Ricerca sul Cancro* (Italian Association for Cancer Research).

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