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The burden of occupational cancer in Great Britain

Breast cancer

Prepared by the **Institute of Environment and Health**, the **Institute of Occupational Medicine** and **Imperial College London** for the Health and Safety Executive 2012

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Breast cancer

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The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer was the attributable fraction (AF) being the proportion of cases that would not have occurred in the absence of exposure; and the AF was used to estimate the number of attributable deaths and registrations. The study involved obtaining data on the risk of the cancer due to the exposure of interest, taking into account confounding factors and overlapping exposures, as well as the proportion of the target population exposed over the relevant exposure period. Only carcinogenic agents, or exposure circumstances, classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens were considered. Here, we present estimates for cancer of the breast that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005. Due to the dominance of female breast cancer and the limited data concerning male breast cancer, this report focuses on breast cancer in women.

The estimated total attributable fraction (female only) for cancer of the breast attributable to occupation overall and associated with shift work (including flight personnel) is 4.56% (95%Confidence Interval (CI)=3.26-5.97), which equates to 555 (95%CI= 397-727) attributable deaths and 1,969 (95%CI=1,407-2,579) attributable registrations.

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EXECUTIVE SUMMARY

The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer used in this project was the attributable fraction i.e. the proportion of cases that would not have occurred in the absence of exposure; this was then used to estimate the attributable numbers. This involved obtaining data on the risk of the disease due to the exposure of interest, taking into account confounding factors and overlapping exposures, and the proportion of the target population exposed over the period in which relevant exposure occurred. Estimation was carried out for carcinogenic agents or exposure circumstances classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens. Here, we present estimates for cancer of the breast that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005. Due to the dominance of female breast cancer and the limited data concerning male breast cancer, this report focuses on breast cancer in women.

Shift work, particularly involving night work, has been classified by the IARC as a probable human carcinogen for cancer of the breast in women. The percentage of working women doing shift work has increased over the last two decades, with current estimates varying from under 5% in industry sectors such as banking and finance to about 20% in transport and communication. About one third of these women work some form of night shift. Shift-work is generally high in occupations associated with health-care, industrial manufacturing, mining, transport, communication, leisure and hospitality sectors and in air transport. Separate estimates have been carried out for general shift/night work and for flight personnel (cabin crew and pilots); the latter are potentially exposed to two potential breast cancer causal factors: night-work/time-zone shift-work and ionising radiation.

Due to assumptions made about cancer latency and working age range, only cancers in ages 25+ in 2005/2004 could be attributable to occupation. For Great Britain in 2005, there were 12,182 deaths in women aged 25+ from breast cancer; in 2004 there were 43,202 registrations for breast cancer in women aged 25+.

The estimated total attributable fraction (female only) for cancer of the breast attributable to occupation overall and associated with shift work (including flight personnel) is 4.56% (95%Confidence Interval (CI)=3.26-5.97), which equates to 555 (95%CI= 397-727) attributable deaths and 1,969 (95%CI=1,407-2,579) attributable registrations of breast cancer in women.

CONTENTS

1 INCIDENCE AND TRENDS

Breast cancer (ICD-10 C50; ICD-9 174-175) includes all cancers associated with the breast, both male and female, including nipple and areola (ICD-10 C50.0; ICD-9 174.0 female; ICD-9 175.0 male); it does not include cancer of the skin of the breast (ICD-10 C43.5, C44.5; ICD-9 172.5, 173.5). Most studies relate to female breast cancer (ICD-10 C50; ICD-9 174); whilst reference will be made to male breast cancer (ICD-10 C50; ICD-9 175), this report will focus on invasive female breast cancer.

Virtually all invasive female breast cancers are adenocarcinomas (derived from glandular tissue), accounting for 10% of all breast tumours (Quinn *et al,* 2001). They predominantly arise in the terminal ductal-lobular units of epithelial tissue and invading the stromal tissue of the breast (Stewart and Kleihues 2003). Ductal carcinoma in situ (DCIS), a non-invasive cancer, is now detected more frequently because of the widespread use of mammography (Cancer Research UK 2007). Lobular carcinoma in situ (LCIS) is also a non-invasive cancer but its presence is associated with an increase in risk of subsequently developing an invasive breast cancer. Most invasive cancers derive from infiltrating ductal carcinomas (75%), with infiltrating lobular cancers comprising 5-10% (Colditz *et al,* 2006). The remaining proportion is derived from medullary, adenoid cystic, mucinous and tubular carcinomas. About 19% of tumours are coded to the upper-outer quadrant of the breast (ICD-10 C50.4; ICD-9 174.4) and a further 16% in other quadrants or the nipple; no anatomic detail was available for 65% of cases (Quinn *et al,* 2001). There are three histological grades used to characterise invasive breast cancers, ranging from well differentiated carcinoma to poorly differentiated; the higher the grade, the poorer the prognosis (Colditz *et al,* 2006).

Tables 1 and 2 (ONS 2000-2006) provide an indication of male and female breast cancer trends over the period from the mid-1990s to the mid-2000s in England and Wales. Whilst registrations of male breast cancer have remained relatively stable over the thirteen year period, with a crude rate of approximately one case per 100,000, female breast cancer incidence has increased from over 30,000 cases per year in 1993 (equivalent to a crude rate of 116 per 100,000 population) to over 38,000 cases in 2005 (crude rate of 148 per 100,000 population) (Table 1). On average, male breast cancer represents approximately 0.22% of male cancer registrations; for women, female breast cancer is the most significant cancer, accounting for about 30% of all female cancer registrations. Trends in mortality appear reversed, with increasing mortality rates in men (66 in 1999 to 81 in 2005) and declining mortality in women (crude rate of 423 deaths per 100,000 in 1999 to 284 deaths per 100,000 in 2005) (Table 2). Table 3 shows breast cancer mortality trends in England and Wales for the period 1971-2000, with male breast cancer mortality remaining relatively stable but female breast cancer declining over recent years from over 20% of all cancer deaths to less than 18%.

In England and Wales since the late 1970s up to the introduction of breast screening, age-standardised incidence for women increased by about 2% per year; with the introduction of screening, rates have frequently followed a sequence of increase followed by decline and then increase as first-time screening identified tumours in earlier age-groups before numbers equalised (Quinn *et al,* 2001). It is notable that there has been an almost continuous increase in risk across successive birth cohorts from the late 19th century (Quinn *et al,* 2001). Mortality from female breast cancer also increased, specifically in the 1950s and 1960s for women aged 50-69. With screening of this age group, however, mortality has fallen by over 20%, a reduction that has been greatly affected by the development of new treatments (tamoxifen and other chemotherapy) and greater awareness among women and doctors (Quinn *et al,* 2001). Age-specific incidence and mortality rates increase steeply after the age of 40, with 80% of cases occurring in women over 50 years old and peaking in the 50-59 age groups, while deaths rise steadily to a peak in the 85 and over group (Cancer Research UK 2007; Quinn *et al,* 2005). The greatest increase in risk occurs just before the menopause. While rates are considerably lower in women aged under 35, breast cancer is the most commonly diagnosed cancer for this age group. Incidence rates are generally 30% higher in more

affluent socio-economic groups than the most deprived, a pattern reflected in the Unites States and with strong lifestyle associations discussed in Section 2. Mortality, however, is positively correlated with deprivation, implying that survival is higher in the more affluent. In England, incidence rates are generally higher than average in the south (not London) and lower than average in the north (Quinn *et al,* 2005). Geographical patterns in mortality are less obvious. Male breast cancer incidence and mortality also show an increase with increasing age, particularly from the 65 and over age groups to a peak for both incidence and mortality at 85 and over.

Table 1: Number of breast cancer registrations in England and Wales 1994, England 1995-2005, by ICD-10 category (and ICD-9 category)

		Total registrations	% Total	Crude rate /100,000		Total registrations	% Total	Crude rate /100,000
Year	Total Cancer Reg*	C50 (175)	C50 (175)	C50 (175)	Total Cancer Reg*	C50 (174)	C50 (174)	C50 (174)
	MALE				**FEMALE**			
1992	109336	191	0.17	0.8	112247	31843	28.37	121.6
1993	109414	248	0.23	1.0	109891	30495	27.75	116.2
1994	112145	189	0.17	0.7	112175	31671	28.23	120.3
1995	103986	216	0.21	0.9	105151	29904	28.44	120.1
1996	104103	202	0.19	0.8	105461	30412	28.84	121.8
1997	104335	232	0.22	1.0	107289	31380	29.25	125.4
1998	106745	269	0.25	1.1	109957	32908	29.93	131.0
1999	108827	272	0.25	1.1	112237	34176	30.45	135.6
2000	111543	206	0.18	0.9	112066	33829	30.19	134.4
2001	112516	245	0.22	1.0	112134	34347	30.63	136.1
2002	112579	248	0.22	1.0	111210	34319	30.86	135.3
2003	112732	295	0.26	1.2	114740	36509	31.82	143.5
2004	117805	272	0.23	1.1	115816	36939	31.89	144.6
2005	119625	250	0.21	1.0	119352	38212	32.02	148.6
Ave.	**109756**	**238**	**0.22**	**0.97**	**110749**	**33353**	**29.94**	**131.04**

*All cancers excluding non-melanoma skin cancer (NMSC)
Source: adapted from ONS (2006a; 2005a,b; 2004a; 2003a; 2002a,b; 2001a; 2000a))

Table 2: Number of breast cancer deaths in England and Wales 1999-2005, by ICD-10 (and ICD-9) category

		Total cancer deaths	% Total	Crude rate /100,000		Total cancer deaths	% Total	Crude rate /100,000
Year	Total Deaths*	C50 (175)	C50 (175)	C50 (175)	Total Deaths*	C50 (174)	C50 (174)	C50 (174)
	MALE				**FEMALE**			
1999	264299	66	0.02		291819	11604	3.98	423
2000	255547	70	0.03		280117	11363	4.06	411
2001	252426	81	0.03	3	277947	11557	4.16	419
2002	253144	81	0.03	3	280383	11476	4.09	409
2003	253852	67	0.03	2	284402	11209	3.94	293
2004	244130	59	0.02	2	268411	10972	4.09	285
2005	243324	81	0.03	2	269368	11040	4.10	284
Ave.	**252389**	**72**	**0.03**	**2.4**	**278921**	**11317**	**4.06**	**361**

*All causes including all cancers
Source: adapted from ONS (2006b; 2005c; 2004b; 2003b; 2002c; 2001b; 2000b)

Table 3: Cancer mortality trends 1971-2000 in England and Wales and proportions associated with all categories of malignant neoplasms of the breast (ICD-10 50, C68; ICD-9 174-175).

	Male			Female		
Year	**Total neoplasms**	**All breast neoplasms**	**% Total**	**Total neoplasms**	**All breast neoplasms**	**% Total**
1971-1975	326838	391	0.12	279710	56635	20.25
1976-1980	343180	419	0.12	298261	59756	20.03
1981-1985	359493	436	0.12	320635	64413	20.09
1986-1990	374103	450	0.12	343106	68757	20.04
1991-1995	374029	431	0.12	342716	65824	19.21
1996-2000	355943	346	0.10	330414	58885	17.82

Source: ONS (2001b)

In Great Britain, female breast cancer is the most common cancer in women, with 43,225 new cases diagnosed in 2004, accounting for 1 in 3 of all malignant female cancers (ISD 2005; ONS 2006a; WCISU 2008; Table 4). Between 1980 and 2004, the incidence rate of female breast cancer in Great Britain increased by 53% (ISD 2005; ONS 2006a; WCISU 2008). As for England and Wales, incidence rates in Great Britain have been greatly influenced by the introduction of national breast screening programmes. Breast cancer in men is extremely rare, with 322 cases diagnosed in Great Britain in 2004 (ISD 2005; ONS 2006a; WCISU 2008; Table 4); it is unclear whether this is due to inherent low incidence or as a consequence of low rates of diagnosis. Female breast cancer is now the second most common cause of cancer mortality in women in Great Britain after lung cancer, accounting for almost 1 in 5 of all cancer deaths and 5% of all deaths in women in the 1990s; for women aged 35-54, breast cancer accounts for 32% of all deaths (Cancer Research UK 2007; Quinn *et al,* 2005). In 2005 in Great Britain, there were 12,184 deaths from female breast cancer, compared to 88 from male breast cancer (ISD 2005; ONS 2006b; Table 5). Across the UK, however, there has been a 33% decline in age-standardised breast cancer mortality, from 42 to 28 per 100,000 women, since 1989 (Cancer Research UK 2007). The reduction in breast cancer mortality rates is likely to have several causes including screening, increasing specialisation of care and the widespread adoption of tamoxifen treatment since 1992.

In the late 1980s, five-year survival in Great Britain from female breast cancer was around 65%, and better than for the other major cancers in women (lung, colorectal, ovary and cervix). This represented an increase on the 52% survival rate determined for the period 1971-1975 (Quinn *et al,* 2001, 2005; Cancer Research UK 2007). However, survival is worse the later the stage of the disease at diagnosis; so whilst stage I diagnoses achieved 85% five-year survival in the 1980s, stage IV survival was only 20%. This 1980 level was one of the lowest survival rates in the world. By the late 1990s, overall five-year survival was around 80% in England, Wales and Scotland (Quinn *et al,* 2005). Survival from breast cancer differs from most other cancers in that women diagnosed when under 40 years of age have worse survival than older women; women aged 50-69 have the highest five-year survival rates possibly attributable to mammographic screening and earlier diagnosis (Cancer Research UK 2007; Quinn *et al,* 2005). While there are no marked regional differences in survival in Great Britain, survival rates are higher for women from more affluent areas (Quinn *et al,* 2001; Coleman *et al,* 2004). Studies have shown that the reason for this difference appears to be cancer stage at presentation, with women from more deprived areas presenting with locally advanced or metastatic disease (Macleod *et al,* 2000).

While cervical cancer is more frequent in some developing countries, breast cancer is the most common cancer in women worldwide with over 1 million new cases diagnosed every year (Stewart and Kleihues 2003; Quinn *et al,* 2001). Across male and female cancers, it is ranked second in

incidence and fifth in mortality across all cancers (Colditz *et al,* 2006), with the proportion highest in women in western, developed, affluent countries. Over 400,000 deaths annually are attributable to female breast cancer, representing 1.6% of all female deaths (Stewart and Kleihues 2003). Incidence and mortality are highest in USA, Canada, Europe, the Nordic countries, Australia, Singapore, Japan and some parts of South America, especially Uruguay and Argentina. In Europe, the highest rates of female breast cancer occur in the UK and Ireland, followed by other northern European countries; rates in southern Europe, particularly southern Italy, are lower than the European average (Smans *et al,* 1992; Zatonski *et al,* 1996). Low rates are found in African and Asian populations; Native Americans in New Mexico have been identifed by population-based registries as having one of the lowest global rates (Parkin *et al,* 1997). Singapore, Japan and, more recently, urban China, were traditionally low incidence areas but increases since 1950s, thought to be associated with growing economies and increases in women in the industrial workforce, have raised the rates to levels in the US and northern Europe (Colditz *et al,* 2006; Hoover 1996; Jin *et al,* 1993). Studies of migrant populations have found that women migrating from low-risk to high-risk regions acquire the rate of the host country within two to three generations indicating that lifestyle and environment, rather than genetic differences, are greater potential causal factors (Colditz *et al,* 2006; Stewart and Kleihues 2003). In the period 1975 to 1990, the number of breast cancer cases worldwide almost doubled, with the largest increases often shown by registries having previously recorded the lowest rates of disease, namely in Asia, Africa and some parts of Europe (Peto *et al,* 2000; Parkin *et al,* 1997); the smallest increases tend to be in places previously associated with higher rates, North America and northern Europe. Generally, incidence is higher in urban areas compared to rural. Mortality rates in high incidence areas are generally falling due to improved screening and treatment practices, although this does vary by age and race; however, in almost all developing countries exhibiting a recent increase in female breast cancer incidence, mortality is also increasing reflecting growing rates of incidence (Parkin *et al,* 2001). Globally, incidence and mortality increase with age; while mortality continues to increase after menopause, the rate of increase of breast cancer incidence slows from a peak before menopause (Colditz *et al,* 2006; Pike *et al,* 1993).

Table 4: Number of registrations from breast cancer (ICD-10 C50; ICD-9 174-175), 2004.

	England	Wales	Scotland	Total
Males	272	19	30	321
Females	36939	2369	3940	43248
All	37211	2388	3970	43569

Source: ISD2005; ONS 2006a; WCISU 2008

Table 5: Number of deaths from breast cancer (ICD-10 C50; ICD-9 174-175), 2005.

	England and Wales	Scotland	Total
Males	81	7	88
Females	11040	1144	12184
All	11121	1151	12272

Source: ISD 2005; ONS 2006b

2 OVERVIEW OF AETIOLOGY

2.1 INTRODUCTION

Due to the dominance of female breast cancer and the limited data concerning male breast cancer, this report will focus on the aetiologies of breast cancer in women. Despite the very limited data concerning male breast cancer, it would appear to have a different aetiology to female breast cancer. Furthermore, unless otherwise stated, any discussion will refer to invasive female breast cancer rather than in situ disease (CDIS or LCIS) although the aetiologies of both are suggested to be similar (Trentham-Dietz *et al,* 2000).

There exists considerable evidence of associations between various risk factors and breast cancer incidence. Most of the known risk factors relate to a woman's reproductive history, including early menarche, late first pregnancy, low parity and late menopause. This is supported by evidence from animal studies showing that mammary tumours do not develop after ovaries have been removed, even after exposure to carcinogens, emphasising the importance of the affects of hormonal factors in mammary carcinogenesis (Russo and Russo, 1996; 1998). For humans, associated factors include exogenous hormones (oral contraceptive use and hormone replacement therapy). Genetic factors are also important, as are certain lifestyle factors. More recently, there is evidence of an occupational association with female breast cancer. Each of these risk factors is considered in more detail, although occupational risk factors are the focus of this report.

Earlier age at menarche has been consistently linked with increased risk of both premenopausal and postmenopausal breast cancer, with risk declining for every one-year delay in menarch by 10-24% (Kelsey *et al,* 1993; Bernstein 2002). The period between menarche and onset of regular menstrual cycles has also been identified as a possible risk factor, with risk increasing for shorter time periods (Henderson *et al,* 1981). Shorter menstrual cycle length is associated with greater risks of breast cancer, probably due to more frequent oestrogen and progesterone exposures (Kelsey *et al,* 1993). The risk of breast cancer is increased by about 50% in nulliparous compared to parous women, particularly in the 40-45 years age group (Colditz *et al,* 2006; Smans *et al,* 1992). Risk increases with increasing age at first birth up to age 35 years when risk is equal to or higher than nulliparity (Ewertz *et al,* 1990). It has been estimated that every year of increase in age at first birth increases the relative risk by 3.5% (Trichopoulos *et al,* 1983). Hence, parity at an early age can be considered to reduce lifetime risk of breast cancer, reflecting the final maturation of the breast with hormonal exposures during first pregnancy (Kelsey *et al,* 1993). However, risk reduction is not immediate, taking 10-15 years to manifest, with risk immediately following first pregnancy higher and related to the interval between menarche and first birth (Pike *et al,* 1983; Rosner *et al,* 1994). Multiparity and more closely spaced births are associated with lower lifetime risk of breast cancer (Rosner *et al,* 1994; Trichopoulos *et al,* 1983). Breastfeeding is also associated with breast cancer risk reduction with evidence suggesting that relative risk decreases by 4.3% for every 12 months of breastfeeding, in addition to a 7% reduction for each birth (Lane-Claypon 1962; CGHFBC, 2002a). The available evidence does not support an association between induced abortion and breast cancer risk (Colditz *et al,* 2006). The rate of increase in breast cancer incidence slows at menopause, hence the earlier the age at menopause, the lower the risk (Lilienfeld 1956; Trichopoulos *et al,* 1972). Artificial menopause has a greater risk reduction effect due to immediate cessation of ovarian function (Bernstein 2002). Generally, endogenous hormone levels, particularly oestrogens and oestrogen metabolites, androgens, progesterone and prolactin, have been found to have a positive association with post-menopausal breast cancer risk, and insulin-like growth factor I (IGF-I) positively associates with pre-menopausal breast cancer; oestrogen and testosterone have particularly significant associations with elevated breast cancer risk (Colditz *et al,* 2006).

It has been suggested that prolonged use of oral contraceptives (more than 5 years) is associated with elevated breast cancer incidence in women under 35 years through the elevation of oestrogen and progestogen hormone levels (Prentice and Thomas 1987; Bernstein 2002). Risk rapidly declines when oral contraceptive use is stopped. In a combined reanalysis including upwards of

53,000 breast cancer cases, the relative risk for current users of oral contraceptives compared to never users was 1.24, with relative risks declining for women 1-4 years after stopping and 5-9 years of 1.16 and 1.07 respectively (IARC 2007; CGHFBC, 1996). The use of non-contraceptive synthetic oestrogens, particularly diethylstilbestrol (DES) prescribed during the 1940s to early 1970s to reduce the likelihood of miscarriage, have also been associated with increased rates of breast cancer in women prescribed the drug and their daughters (Palmer *et al,* 2006). While the International Agency for Research on Cancer (IARC) classify the combined oestrogen-progestogen oral contraceptive as a Group 1 carcinogen (IARC 2007), progestogen-only contraceptives are considered Group 2B carcinogens (IARC 1999a) Furthermore, use of menopausal hormone replacement therapy (HRT) increases the risk of breast cancer in the higher risk age categories by as much at 50% (Key and Pike 1987), specifically for users of long duration and current users. Ever users compared to never users show little or no increased risk. Among women who had used HRT within the previous five years (compared with never users), the relative risks for duration of use were 1.1 for 1-4 years, 1.3 for 5-9 years, 1.2 for 10-14 years, and 1.6 for 15 years or more of use. No significant increase in breast cancer risk was reported for women who had stopped using HRT five or more years ago, regardless of duration of use, and no significant difference in risk was found for type of HRT and dose used (CGHFBC, 1997). This is supported by earlier work that noted a positive correlation for invasive breast cancer in current users of 5-15 or more years duration (Schairer *et al,* 1994). Risk was not confounded by reproductive history, alcohol consumption, smoking or family history of breast cancer; low body mass index HRT users of five or more years duration were associated with higher risk (Huang *et al,* 1997; Schairer *et al,* 2000). Use of oestrogen/progestogen HRT poses greater risk than oestrogen only HRT (IARC 2007; Chlebowski *et al,* 2003; Bergkvist *et al,* 1989), with one UK study reporting a highly significant relative risk of breast cancer for current users of oestrogen only preparations compared to never users of 1.30 (95% CI 1.22-1.38), whilst the highly significant relative risk for current users of oestrogen plus progestogen combinations was 2.00 (95% CI 1.91-2.09) (Banks *et al,* 2003). IARC considers both oestrogen-only and oestrogen-progestogen HRTs to be Group 1 carcinogens (IARC 1999a, 2007). The effects of different oestrogen/progestogen formulations, doses and regimens/schedules on breast cancer risk have not yet been fully assessed (Colditz *et al,* 2006). Furthermore, a number of commonly used substances suspected of having endocrine disrupting properties have been shown to increase incidence of mammary tumours in experimental animals (Brody and Rudel, 2003).

One of the strongest independent risk factors for breast cancer is mammographic density, the radiographic appearance of the breast on a mammogram. Women with the greatest mammographic densities are four- to six-times more likely to develop breast cancer than those with little or no density (Byrne 1997). It is also worth noting that regular screening through mammography and clinical breast examination is highly effective at reducing risk of breast cancer mortality (as opposed to incidence), with women regularly screened having a 25-30% lower risk of dying from breast cancer than those not regularly screened (Smith *et al,* 2003).

There has been considerable work on the association between breast cancer and diet, including dietary intake of total, saturated, monounsaturated or polyunsaturated fat (Prentice *et al,* 2006; Hunter *et al,* 1996; Boyle and Leake 1988). While animal studies have frequently demonstrated a positive association between the intake of various types of fat and breast cancer incidence, human epidemiologic studies tend not to identify such associations (Colditz *et al,* 2006; Viguera Salvago *et al,* 2003). However, it is possible that there exists an inverse relationship between consumption of vegetable fat and breast cancer, with high intakes of olive oil and other monounsaturated fats associated with low breast cancer rates (Cho *et al,* 2003; Martin-Moreno *et al,* 1994). As fibre inhibits re-absorption of oestrogens in the gastro-intestinal tract, a high fibre diet has been suggested to lower breast cancer risk but results of epidemiologic studies are inconclusive (Goldin *et al,* 1982). The protective effect of a diet rich in fruit and vegetables, as well as diets high in micronutrients, has frequently been reported for breast cancer; although there is some evidence of risk reduction through high folate intake and green vegetables, the association is suggestive rather than conclusive (Zhang *et al,* 2003; Smith-Warner *et al,* 2001; Katsouyanni *et al,* 1986). Phytoestrogen intake, principally through a diet rich in soy products, have the potential to increase

breast cancer rick particularly in premenopausal women (Petrakis *et al,* 1996; McMichael-Phillips *et al,* 1998), but much more work is required to clarify this possible relationship. Diets rich in cooked meat, particularly well-done meats, are high in heterocyclic aromatic amines such as 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) have also been cited as causal factors for breast cancer (DeBruin and Josephy 2002).

An association between smoking, and/or exposure to passive smoke, and breast cancer is unclear (Hanaoka *et al,* 2005; Johnson 2005; Baron 1984; Ewertz 1990), although an association between early-life exposure to polyaromatic hydrocarbons (PAHs), such as those found in environmental tobacco smoke, has been associated with increased post-menopausal breast cancer in women (OR 2.42; Bonner *et al,* 2005). Alcohol consumption and breast cancer have been evaluated in more than 100 studies and frequently significant causal associations have been identified between increasing alcohol intake and breast cancer risk (Baan *et al,* 2007; Longnecker et la. 1994). A pooled analysis of 53 studies on more than 58,000 women with breast cancer showed that a daily consumption of 50 g of alcohol (about 5 drinks) is associated with a relative risk of 1.5 (95% CI 1.3-1.6) compared to non-drinkers (CGHFBC, 2002b). Recent adult drinking appears to be more important than early drinking, suggesting that reductions in mid-life may reduce breast cancer risks (Longnecker *et al,* 1995). Also, increased folate consumption appears to mitigate the excess risk caused by alcohol consumption (Zhang *et al,* 2003). Viral infections, particularly by the Epstein-Barr virus, have been suggested to be a possible aetiologic factor for breast cancer (Coyle 2004). Solar radiation, however, may provide a protective effect, with increased levels of vitamin D production suggested to be one mechanism of action (Coyle 2004).

Height is positively correlated to breast cancer risk in both pre- and post-menopausal women (Van den Brandt *et al,* 2000). Height is associated with childhood energy intake and age of puberty (with oestrogen linked to epiphysial plate closure), both factors that have also been linked to breast cancer incidence (Colditz *et al,* 2006; Robsahm and Tretli 2002). The risk of breast cancer in Western populations appears to rise with increasing body mass index (weight divided by height) among post-menopausal women but is inversely associated in pre-menopausal women; both associations are influenced by endogenous hormone levels, with adipose tissue the major source of post-menopause oestrogen (Rapp *et al,* 2005; Lahmann *et al,* 2003; Ursin *et al,* 1995; Hunter and Willett 1993). In non-Western populations, the inverse relationship between weight and pre-menopausal women is not observed and the association with post-menopausal women is stronger (Pathak and Whittemore 1992). Physical activity has also been positively associated with breast cancer risk but the underlying mechanisms have not been fully elucidated (Friedenreich *et al,* 1998; Gammon *et al,* 1998). Other factors including exposure to persistent organochlorines, use of under arm deodorant/antiperspirant and silicone breast implants, do not appear to be major breast cancer risk factors (Laden *et al,* 2001; Mirick *et al,* 2002; Brinton and Brown 1997; IARC 1999b). Pre-natal exposure to elevated maternal oestrogen levels have been suggested to increase breast cancer risk at later ages, as do lifestyle factors at young ages (lower physical activity, low BMI, etc.); women breast fed as infants have a reduced risk (Trichopoulos, 1990; Baer *et al,* 2005; Marcus *et al,* 1999). Exposure to ionising radiation is associated with increased breast cancer risk as shown in studies of the survivors of the atomic bombings (Tokunaga *et al,* 1994; UNSCEAR 2000, 2008). These studies reveal that the largest breast cancer risks were for those exposed to radiation as children (pre-puberty) and young adults, with risks declining with age (UNSCEAR 2008). Socio-economic status has been shown to be inversely correlated with female breast cancer (Brody and Rudel, 2003); this is particularly evident in the breast cancer excesses seen for white collar workers as opposed to blue collar workers (Van Loon *et al,* 1994). In the United States, a number of racial and ethnic differences in breast cancer incidence and mortality have been identified that are not associated with socio-economic status (Colditz *et al,* 2006). Incidence rates are higher but mortality lower in white women compared to black women; breast cancer rates in Asian, Hispanic and Native American women in the US are considerably lower than those of non-Hispanic white and black women (Ries *et al,* 2005).

Family history of breast cancer increases the risk of breast cancer by 1.5-3 times, particularly in premenopausal women with a first-degree relative with breast cancer at premenopausal ages (Macklin 1959). On average, 5-10% of breast cancers are due to inherited genetic mutations and are frequently characterised by early age onset and excess of bilateral breast cancer (Bennett *et al,* 1999). Mutations to the BRCA genes are estimated to cause 2-5% of all breast cancers, with mutation carriers having an 80% risk of developing the disease (Easton *et al,* 1995). As well as other inherited mutations of the p53 gene, PTEN gene and ATM gene (in ataxia telangiectasia sufferers), risk of breast cancer are increased by genes with low penetrance (Colditz *et al,* 2006). While expected to confer only a small increase in risk, a much larger population will be affected, with a number of major gene classes involved in oestrogen biosynthesis (from cholesterol) and metabolism, carcinogen metabolism, and DNA damage and repair identified.

An association between the use of electric blankets and breast cancer incidence has been suggested (Vena *et al,* 1991; Gammon *et al,* 1998; Kabat *et al,* 2003; Sandler 2003; Laden *et al,* 2000). The current in the electric blanket generates an electromagnetic field, and electromagnetic fields (EMF) have been cited as one possible breast cancer causal factor (see Section 2.2.3 below). However, residential exposure to electromagnetic fields through the use of electric blankets does not appear to affect breast cancer risk (Davis *et al,* 2002; Kabat *et al,* 2003). Residential proximity to power lines, another EMF source, do not reveal consistent associations with breast cancer risk (Kheifets *et al,* 1999).

There have been very few studies evaluating the aetiologies of male breast cancer. Sasco *et al,* (1993) report a meta-analysis that identified a positive correlation between male breast cancer and prostate cancer as well as associations between male breast cancer incidence and marital status, religion, previous breast and testicular pathology, gynaecomastia, previous liver diseases, and family history of breast cancer. However, they report a lack of information concerning possible links with reproductive history, occupation and anthropometric variables among other factors. Overall, male breast cancer shows a similar epidemiology to female breast cancer, with hormonal status having a major role and genetics also being a key risk factor. The lack of data concerning male breast cancer is a recognised phenomenon resulting from its relative rarity compared to other cancers (see Tables 1-5) but efforts are being made to rectify this absence of data (Korde et al. 2010).

There are many causes associated with the aetiology of breast cancer, most of them associated with lifestyle, which make confounding of potential occupational factors a real possibility (Swerdlow 2003). Although breast cancer is not generally considered to be occupationally associated, reproductive and lifestyle factors can only account for 50% of incident breast cancers; environmental and occupational aetiologies must therefore be considered (Goldberg and Labreche 1996).

IARC have assessed the carcinogenicity of a number of substances and occupational circumstances with those classified as Group 1 having sufficient evidence in humans and those classified as Group 2A having limited evidence in humans. Shift work has very recently been classified as a Group 2A exposure circumstance for breast cancer (Table 6; Straif *et al,* 2007;). Occupational exposure to ethylene oxide has also been suggested as a possible casual factor for breast cancer (Grosse *et al,* 2007). Siemiatycki *et al,* (2004) do not include breast cancer in their consideration of occupationally associated cancers.

Table 6: Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Vols 1-98, into Groups 1 and 2A, which have female breast cancer as the target organ.

Agents, mixture, circumstance	Main industry, use; or, suspected substance	Evidence of carcinogenicity in humans	Strength of evidence	Other target organs
Group 1: carcinogenic to humans				
Agents, groups of agents				
None specified				
Exposure circumstances				
None specified				
Group 2A: probably carcinogenic to humans				
Agents, groups of agents				
None specified				
Exposure circumstances				
Shift-work	Healthcare; industrial manufacturing; mining; transport; communication; leisure and hospitality	Limited	n/a	

Source: adapted from Siemiatycki *et al,* (2004) and IARC (In prep. B)

The Occupational Health Decennial Supplement (Drever 1995) examined cancer incidence (1981-1987) in England and cancer mortality (1979-1980, 1982-1990) in England and Wales in men and women aged 20-74 years. Table 7a shows breast cancer incidence and mortality for both women and men. It has been suggested that elevated incidence and mortality from female breast cancer occurs in occupations traditionally associated with unmarried women with no children or late age at first birth, such as teaching and certain healthcare professions (Drever 1995; Bernstein *et al,* 2002; Andersen *et al,* 1999). Women teachers have significantly high proportional registration risks (PRRs) and high proportional mortality ratios (PMRs) for breast cancer. Whilst physiotherapists have a high PRR, the PMRs are not significant or show a deficit of breast cancer mortality in other healthcare professions such as nursing. Administrators and office workers also demonstrate elevated mortality from female breast cancer. Other occupations, including postal workers, paper manufacturers, compositors and employment in the textile industry (specifically as tailors, sewers and associated occupations), suggest an association between general but non-nightwork shift-work and mortality from female breast cancer. Only 30% of deaths occurring at ages 20-74 in women in England and Wales during the period 1979-1990 had occupation recorded on their death certificate due generally to the lack of consistent employment history for many women (Drever 1995). There are elevated levels of incidence and mortality from male breast cancer in builders and drivers of heavy machinery indicating a possible association between occupations in the construction industry and male breast cancer. Table 7b provides more recent data regarding occupation and mortality from female breast cancer (Coggon *et al,* 2009). The occupations identified for the period 1991-2000 are similar to those shown in Table 7a for women, showing predominance in office workers, teachers, administrators and certain textile workers. A stronger association is now seen with the healthcare profession whilst the more industry/manufacturing-based occupations no longer feature. In particular, medical radiographers have been found to have a high PMR for the 1991-2000 period, indicating the potential affects of occupational exposure to X-radiation (ionizing radiation) in the medical professions and a possible exposure to ethylene oxide as a sterilising agent.

Table 7a: Job codes with significantly high PRRs and PMRs for breast cancer. Men and women aged 20-74 years, England, 1981-1987 (Drever 1995).

Job group		Registration	PRR*	95% CI	Deaths	PMR**	95% CI
SIC code	Description	(1981-87)			(1979-1980 and 1982-90)		
Men (male breast cancer ICD-9 175)							
169	Builders etc.				16	197	6-89
186	Mechanical plant drivers	4	829	226-2125			
187	Crane drivers	5	336	109-784			
Women (female breast cancer ICD-9 174)							
008	Government administrators				117	129	106-154
009	Other administrators				436	111	101-122
010	Teachers in higher education				167	133	113-154
011	Teachers nec	1942	118	113-123	2404	128	123-133
017	Nurses#				2245	85	82-89
020	Physiotherapists	71	128	100-162			
031	Draughtsperson				44	147	107-197
052	Hairdressers				249	114	100-129
053	Office workers and cashiers				10522	106	104-108
054	Postal workers				110	122	100-147
060	Other service personnel	3003	103	100-108			
079	Paper manufacturers				13	238	127-407
080	Book binders				82	126	100-156
094	Compositors				12	214	111-374
098	Tailors and dressmakers				326	120	107-133
100	Sewers and embroiderers				835	109	101-116
190	Storekeepers				195	117	101-134

*$p<0.05$ based on at least 3 registrations; adjusted for age, social class and registration region.

**$p<0.05$ based on at least 3 registrations; adjusted for age and social class.

#Breast cancer deficit.

Table 7b: Job codes with significantly high PMRs for breast cancer. Women aged 20-74 years, England 1991-2000.

Job group		Observed mortality	Expected mortality	PMR**	95% CI
SIC code	Description	(1991-2000)			
Women					
001	Lawyers	122	100.2	121.7	101-145.3
003	Personnel Managers etc	208	177.1	117.5	102-134.6
008	Government administrators	177	147.4	120.1	103-139.1
011	School Teachers	2792	2154.2	129.6	125-134.5
012	Vocational Trainers, Social Scientists etc.	331	293.0	113.0	101-125.8
019	Medical Radiographers	58	42.0	138.1	105-178.5
021	Other Health Professions	327	287.9	113.6	102-126.6
037	Other Technicians	271	228.2	118.8	105-133.8
053	Office Workers and Cashiers	11717	11153.5	105.1	103-107
060	Other Service Personnel	3656	3454.5	105.8	102-109.3
098	Tailors and Dressmakers	233	195.8	119.0	104-135.3
100	Sewers and embroiderers	729	655.1	111.3	103-119.7

Source: Coggon *et al.* (2009) Occupational mortality in England and Wales, 1991-2000

2.2 OCCUPATIONAL EXPOSURES

IARC have described associations between female breast cancer incidence/mortality and occupational exposures to shift working patterns (Table 6). However, a number of other exposure circumstances and agents, including ionising radiation, have also been discussed by IARC and other workers and hence will be evaluated in this report. In particular, airline cabin crew (hereafter referred to as flight personnel) will be considered to be a separate category due to potential overlap of shift-work and ionising radiation. A number of reports link increased risk of male breast cancer with occupations in a range of industries e.g. newspaper printing, soap and perfume making, as well as occupations in newspaper works, blast furnaces, steel works, rolling mills, motor vehicle manufacturing and in jobs which involve exposure to low frequency electromagnetic frequencies (Mabuchi *et al*. 1985). However, evidence is not consistent across reports (Sasco *et al*. 1993) and there have yet to be any studies published reporting an association between male breast cancer and shift work, which is the one Group 2A occupational carcinogen identified by IARC as associated with female breast cancer. Unless otherwise stated, all reference to breast cancer and occupational exposures will be to female workers.

2.2.1 GENERAL SHIFT WORK

A high proportion, approximately 15-20%, of the working population (men and women) in Europe and North America are involved in shift-work that involves night-work (Straif *et al,* 2007), described as working at least one night a month and at least two hours between 2200 and 0500. In Europe, 10% work 1-5 nights per month, 10% work more than 5 nights per month and 0.4% work permanent night shifts. Shift-work is generally high in occupations associated with health-care, industrial manufacturing, mining, transport, communication, leisure and hospitality sectors, and can account for more than 30% of employment in these areas. The percentage of working women doing shift work has increased over the last two decades, with current estimates varying from under 5% in industry sectors such as banking and finance to about 20% in transport and communication. About one third of these women work some form of night shift. While not all shift-work involves periods of night-time employment, it is the night-work that is most disruptive for the circadian clock. Exposure to light-at-night disturbs the circadian system causing alterations to sleep-activity patterns, increased oxidative stress, suppression of melatonin production, and deregulation of circadian genes involved in cancer-related pathways (Straif *et al,* 2007; Stevens *et al,* 2007). Inactivation of the circadian mouse Period gene (mPer2) promotes tumour development (Fu *et al,*

2002); in human breast and endometrial tumours, the expression of Period (Per) genes is inhibited (Straif *et al,* 2007; Chen *et al,* 2005). Furthermore, immunodeficiency results from sleep deprivation and the ensuing melatonin suppression, while other changes to diet and lifestyle (alcohol consumption/smoking) may also be associated with night-work (Straif *et al,* 2007; Everson 1993; Nelson 2004). Stevens (1987) first put forward the hypothesis that exposure to light-at-night might lead to increased female breast cancer risk via perturbation of melatonin homeostasis (Cohen *et al,* 1978). Two studies report that the pineal hormone melatonin inhibits the growth of breast cancer *in vivo* and *in vitro* (Tamarkin *et al,* 1981; Narito and Kudo 1985) providing protective action (Brzezinski 1997). The IARC Working Group have concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Group 2A) on the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves night-work" and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" (Straif *et al,* 2007). IARC consider the main cancer site affected by light-at-night to be the female breast but may also include prostate.

Most work concerning the potential carcinogenic effects of light-at-night have identified melatonin secretion as a key causal factor (Blask *et al,* 2005). Ocular exposure to light-at-night, when the production of melatonin is at its physiological maximum, suppresses normal nocturnal melatonin production in the pineal gland. Studies in experimental animals have shown that uninterrupted ocular exposure to visible light increases the risk of mammary cancer, while pinealectomy boosts tumour growth and exogenous melatonin administration has an oncostatic effect (Tamarkin *et al,* 1981; Musatov *et al,* 1999; Cini *et al,* 1998; Mocchegiani *et al,* 1999; Anisimov *et al,* 1997; Anisimov *et al,* 1999; Anisimov 2003). A number of mechanisms to explain the oncostatic activities of melatonin have been suggested spanning a wide range of immunomodulating actions and suggesting an association between decreased melatonin production and increased levels of reproductive hormones and/or antioxidant properties (Megdal *et al,* 2005; Hansen 2001a; Antunes *et al,* 1999). Totally blind women, unable to detect light through the eyes and hence having abnormal melatonin rhythms, have an approximately 50% lower relative risk of breast cancer compared to sighted women (Hahn 1991; Coleman and Reiter 1992; Sack *et al,* 1992; Feychting *et al,* 1998). Pukkala *et al,* (2006) and Verkasalo *et al,* (1999) found that the risk of breast cancer apparently decreases as the degree of visual impairment increases but biomarker studies of 6-sulphatoxymelatonin indicate that the 24-hour secretion pattern of melatonin does not correlate with the level of visual impairment (Lockley *et al,* 1997; Klerman *et al,* 2001). Furthermore, one prospective study of urinary concentrations of 6-sulfatoxymelatonin in 24-hour urine samples did not find a difference between breast cancer patients and their controls (Travis *et al,* 2004), although a second prospective study indicated that the odds ratio for breast cancer decreased as levels of 6-sulfatoxymelatonin in morning urine samples increased (Schernhammer and Hankinson 2005). A number of studies have shown patterns of lower concentrations of urinary 6-sulfatoxymelatonin among night-workers, both mixed and fixed night shifts, compared to day-shift workers (Hansen *et al,* 2006; Borugian *et al,* 2005; Schernhammer *et al,* 2004). Lewy *et al,* (1980) and McIntyre *et al,* (1989) report that exposure to relatively weak light of about 200-400 lux, equivalent of artificial lighting, during night-time quickly decreases melatonin secretion; more recent work suggests that a threshold level of 30 lux of white light is sufficient for melatonin suppression (Figueiro *et al,* 2006). Outdoor light levels during daylight are approximately 10,000 lux compared to 100-300 lux from artificial lighting within offices and hospitals (day and night) and 0.1-5 lux when asleep (Figueiro *et al,* 2006). Further work is required to ascertain the biological mechanisms underlying exposure to light-at-night and melatonin secretion, and their associations with increased breast cancer risk, particularly in fixed/permanent compared to non-fixed/rotating shift-workers (Schernhammer *et al,* 2001).

Nurses and flight personnel are the main occupational groups considered in epidemiological studies of shift workers. Descriptive studies among nurses have indicated that nurses have a higher risk of breast cancer when compared with the general female population (Andersen *et al,* 1999; Morton 1995; Petralia *et al,* 1998; Lie and Kjaerheim 2003). A review by Lie and Kjaerheim (2003) of predominantly registry-based studies assessed the association between different cancers among

female nurses and occupational exposures, finding an excess of breast cancer that suggests a link to occupation. The study notes that grouping together different workplace nursing jobs under "nurses" potentially obscures occupational causal factors, which may be considered to include shift-work. Despite this, there does appear to be an association between employment as a nurse and slightly elevated risks of developing breast cancer (SIR=1.14; 95% CI 1.09-1.19) (Lie *et al,* 2007). Franzese and Nigri (2007) report a correlation between breast tumour onset and alterations in blood melatonin levels in nurses working night shifts, stating that there is a significant risk of breast cancer in this occupational group. However, Dimich-Ward *et al,* (2007) did not generally find a significant elevation in breast cancer incidence (RR=1.05, 95% CI 0.99-1.11) although more than 25 cumulative years worked as a registered nurse did yield a significant risk for breast cancer of 1.28 (95% CI 1.04-1.59). Flight personnel are considered in a separate section below.

Megdal *et al,* (2005) carried out a systematic review and meta-analysis using 13 studies of breast cancer and night shift workers. An aggregate estimate of 1.48 (95% CI 1.36-1.61) was calculated, including flight personnel and other female night workers. Excluding flight personnel, a relative risk for female night workers of 1.51 (95% CI 1.36-1.68) was determined, based on 6 studies with some adjustment for reproductive history and other confounding factors (Tynes *et al,* 1996; Davis *et al,* 2001; Hansen 2001a; Schernhammer *et al,* 2001, 2005; Lie *et al,* 2006). The authors recognise that incomplete adjustment for confounding remains a limitation of many of the night-work studies, particularly in the case of flight personnel. For this reason, flight personnel are considered separately in another meta-analysis by Erren *et al* (2008) as well as in this report. Erren *et al,* (2008) use seven studies, including the study by O'Leary *et al,* (2006) which does not show a breast cancer risk elevation, to derive a fixed effect summary of 1.4 (95% CI 1.3-1.6) for breast cancer and shift-work (Tynes *et al,* 1996; Davis *et al,* 2001; Hansen 2001a; Schernhammer *et al,* 2001, 2006; Lie *et al,* 2006; O'Leary *et al,* 2006). Both meta-analyses use risk estimates calculated for the longest employment period/greatest lag times and use studies with different definitions of exposure, various exposure periods and different levels of statistical significance.

Of the cohort studies reported in the literature, one of the earliest describes a 10-year follow-up study (1988-1998) of 78,562 US nurses working on rotating night shifts for at least three nights per month in addition to days or evenings (Schernhammer *et al,* 2001). After adjustment for all major confounders associated with lifestyle (including reproductive, dietary and hormone-use history), risk of breast cancer was found to increase significantly with number of years working rotating night shifts with the risk for the longest category of exposure (>30 years) being significantly raised (RR=1.36; 95% CI 1.04-1.78). Risks were higher for postmenopausal women in long-term night-work of 30 years or more (RR=1.36; 95% CI 1.04-1.78) and premenopausal women in long-term employment of 20 or more years (RR = 1.66; 95% CI 0.81-3.40) although a modest association was also found for short- to mid-term employment. Only the association in post-menopausal women was significant. However, the study combined permanent shift-workers with non-shift-workers and hence may underestimate risks associated with shift-work (Swerdlow 2003). While a moderate increase in breast cancer risk among women was reported in the earlier study, a later larger cohort of 115,022 female nurses followed for a 12 year period were found to have a relative risk of 1.79 (95% CI 1.06-3.01) if employed for more than 20 years on a rotating night shift work pattern (Schernhammer *et al,* 2006); permanent night workers were excluded from the study. Schwartzbaum *et al,* (2007) report a census-based cohort study of 2,102,126 male and 1,148,661 female rotating shift workers categorised by shift work percentage and employed between 1960 and 1970, followed till 1989 or the date of their death. Among the women in the census, 3057 described themselves as shift-workers in an interview, defined as being occupations in which at least 40% of the workers either reported that they worked rotating shifts with three of more shifts per 24 hour day or had work hours during the night at least one day preceding the interview week. The most common shift-work occupations among the women were crane operators, delivery drivers and midwifery; there were many more male shift workers than female in a wider variety of occupations. Nurses were not included in the study due to low numbers working night time shifts. Breast cancer incidence was not found to be elevated, with a SIR of 0.94 (95% CI 0.74-1.18) based on the 1970 census, as replicated with other cancer sites looked at in the study, and the authors suggest that a

key factor for the divergence with other findings is the definitions of exposure and exposure duration used and the scale of the study.

A cohort study of 2619 Norwegian maritime radio operators employed between 1920 and 1980 and followed from 1961 to 1991, was used to investigate the effect of radio frequency (RF) electromagnetic fields (EMF) on breast cancer incidence, with shift-work a secondary factor (Tynes *et al,* 1996). In a nested case-control study within the cohort, shift work variables for 50 cases were compared to upwards of four matched controls per case from the same cohort; there were non-significant associations between shift-work and breast cancer at ages 50 and above. For workers exposed to low levels of shift work, defined as less than 3.1 years, the OR was 3.2 (95% CI 0.8-13.7), while for high levels of shift work, described as more than 3.1 to 20.7 years, the OR was determined to be 4.3 (95% CI 0.7-26.0). If employment before the age of 30 years is considered for women aged 50 and over, similar non-significant associations between shift work duration and breast cancer are reported. Thus, if employed before the age of 30 and for up to 2.7 years, an OR of 3.1 (95% CI 0.7-14.2) is reported compared to an OR of 4.6 (95% CI 0.1-7.5) if employment before the age of 30 and for between 2.7 and 17.1 years. No excess was recorded for workers less than 50 years of age, suggesting that exposure to shift work before 30 years of age and a long lag time are key factors in the association with breast cancer incidence. Tynes *et al.* (1996) further report a significant association with breast cancer incidence in the cohort (SIR = 1.5; 95% CI 1.1-2.0), with causal factors cited to be EMF and shift-work exposure. Kliukiene *et al.* (2003) followed the same cohort described by Tynes *et al,* (1996) for a further 11 years, to 2002. A less elevated SIR for all age groups compared to the Tynes *et al,* (1996) value was reported (SIR = 1.30; 95% CI 1.05-1.58) but the impact of shift-work, including overnight work and crossing of time zones, was not elucidated in the accompanying nested case-control study which evaluated cumulative exposure to EMF only. The Tynes *et al.* (1996) and Kliukiene *et al.*(2003) studies have the methodological strength of a nested case-control studies within a good quality cohort study but, as the focus was radio frequency exposure, the relevance of the shift-work categories is poorly explained (IEH 2005; Swerdlow 2003). A Danish population-based case-control study of 7035 breast cancer patients identified four occupations (beverage manufacture, land transport services, catering and air transport services) involving night-work for which an odds ratio of 1.5 (95% CI 1.2-1.7) was determined for women working at least six months in any of the four occupations. For employment exceeding six years, an OR of 1.7 (95% CI 1.3-1.7) was determined, showing a positive trend of increasing breast cancer risk with increasing duration of work at night (Hansen 2001a, 2001b). Significant associations with breast cancer were identified for catering and air transport (inclusion of flight personnel not clarified) as described in Table 8. Lie *et al,* (2006) described a nested case-control study within a cohort of 44,853 nurses first registered in Norway between 1914 and 1980. The odds ratios, adjusted for certain reproductive factors, find that risk increases two-fold if night-work exceeds 30 years (OR = 2.21; 95% CI 1.10-4.45) compared to nursing graduates who did not work nights. For nurses aged 50 and over, the risk of breast cancer was greater than that for nurses younger than 50 years, particularly for longer (15+ years) periods of exposure. This may be indicative of confounding by menopausal/postmenopausal status or suggestive of the importance of lag time between exposure and cancer development. However, inclusion of a lag period of 20 years only resulted in an elevated but non-significant risk for women over 50 years with more than 15 years exposure to night-work (OR = 1.68; 95% CI 0.9-3.12); risk was not noticeably elevated for other age groups or exposure periods.

Table 8: Studies of shift workers and breast cancer.

Reference	Industry/ product	Country	Design	Study size	Results (95% CI; no. of deaths or cases)	Adjusted for confounders
Megdal et al (2005)	Female night workers		Meta-analysis	6 studies	Meta-RR=1.51 (1.36-1.68)	
Erren *et al*, (2008)	Shift-workers		Meta-analysis	7 studies	All studies: FES RR=1.4 (1.3-1.6) Cohort studies: FES RR=1.4 (1.1-1.8) Europe only: FES RR=1.6 (1.3-1.8)	
Tynes *et al*, (1996)	Marine radio/ telegraph operators	Norway	Cohort	2619	All: SIR=1.50 (1.1-2.0; 50) Age <45 yrs: SIR=1.1 (0.6-1.8; 15) Age 45-49 yrs: SIR=1.8 (1.0-3.0; 14) Age 50-54 yrs: SIR=2.5 (1.3-4.3; 13) Age 55+ yrs: SIR=1.2 (0.5-2.4; 8)	Not specified
Schernhammer *et al*, (2001)*	Registered nurses	USA	Cohort	121,701	1-14 yrs – RR=1.08 (0.99-1.18; 134) 15-29 yrs – RR=1.08 (0.9-1.3; 1324) 30+ yrs – RR=1.36 (1.04-1.78; 58) Premenopausal: 1-14 yrs – RR=1.23 (0.97-1.55; 174) 15+ yrs – RR=1.34 (0.77-2.33; 14) Postmenopausal: 1-14 yrs – RR=1.06 (0.97-1.16; 1146) 15-29 yrs – RR=1.05 (0.87-1.27; 120) 30+ yrs – RR=1.36 (1.04-1.78; 58)	Age, age at menarche, parity, age at 1st birth, BMI, family history, benign breast disease, oral contraceptive use, age at menopause, alcohol use, HRT, menopausal status
Kliukiene *et al*, (2003)	Marine radio/ telegraph operators	Norway	Cohort	2619	All: SIR=1.30 (1.05-1.58; 99) Age <50yrs: SIR=1.35 (0.98-1.81; 44) Age 50+yrs: SIR=1.26 (0.95-1.64; 55)	Not specified
Schernhammer *et al*, (2005)‡	Registered nurses	USA	Cohort	115,022	20+yrs – RR=1.79 (1.06-3.01)	Age, age at menarche, parity, age at 1st birth, BMI, family history, benign breast disease, oral contraceptive use, age at menopause, alcohol/smoking status, HRT, menopausal status, physical activity

Reference	Industry/ product	Country	Design	Study size	Results (95% CI; no. of deaths or cases)	Adjusted for confounders
Schernhammer *et al,* (2006)*‡	Registered nurses	USA	Cohort	115,022	1-9 yrs – RR=0.98 (0.87-1.10; 816) 10-19 yrs – RR=0.91 (0.72-1.16; 80) 20+ yrs – RR=1.79 (1.06-3.01; 15)	Age, age at menarche, parity, age at 1st birth, weight change, BMI, height, family history, benign breast disease, oral contraceptive use, age at menopause, alcohol/smoking status, HRT, menopausal status, physical activity
Schwartzbaum *et al,* (2007)	Register-based (not nurses)	Sweden	Cohort	3057 women with likely night-work	In 1970: RR=0.94 (0.74-1.18; 70) In 1969 and 1970: RR=0.97 (0.67-1.40; 28)	Age, socioeconomic status, employment status, county of residence (marital status and urbanisation not considered important)
Tynes *et al,* (1996)	Marine radio/ telegraph operators	Norway	Nested case-control	Cohort=2619 50 cases/259 controls	Women aged 50+: Up to 3.1 yrs – OR=3.2 (0.6-17.3; 6) >3.1 yrs – OR=4.3 (0.7-26.0; 12) Women aged 50+, exposed <age 30: Up to 3.1 yrs – OR=3.1 (0.7-14.2; 6) >3.1 yrs – OR=4.6 (0.1-7.5; 8)	Age, duration of employment, parity, age at 1st birth
Lie *et al,* (2006)§	Nurses	Norway	Nested case-control	Cohort=44,835 537 cases/2148 controls	All ages: 1-14 yrs – OR=0.95 (0.67-1.33; 362) 15-29 yrs – OR=1.29 (0.82-2.02; 101) 30+ yrs – OR=2.21 (1.10-4.45; 24) Age <50 yrs: 1-14 yrs – OR=1.02 (0.60-1.71; 185) 15+ yrs – OR=1.72 (0.56-5.26; 13) Age 50+ yrs: 1-14 yrs – OR=0.86 (0.54-1.37; 177) 15-29 yrs – OR=1.17 (0.68-2.00; 88) 30+ yrs – OR=2.01 (0.95-4.26; 24) Age 50+, 20-yr lag-OR=1.68(0.9-3.1)	Total employment time as a nurse, parity; age at 1st birth considered but not adjusted for; matched by birth year
Davis *et al,* (2001)†	Work history	USA	Case-control	813 cases/793 controls	Ever worked: OR=1.6 (1.0-2.5; 54) <1.2 hrs/week: OR=1.3 (0.5-3.1; 11) 1.2-2.7 hrs/wk: OR=1.4 (0.6-3.2; 13) 2.7-5.7 hrs/wk: OR=1.5 (0.6-3.6; 13) ≥5.7 hrs/week: OR=2.3 (1.0-5.3; 17)	Parity, family history of breast cancer, oral contraceptive use (ever and <5 years), discontinued use of HRT

Reference	Industry/ product	Country	Design	Study size	Results (95% CI; no. of deaths or cases)	Adjusted for confounders
					<3years worked: OR=1.4 (0.6-3.2; 15) ≥3years worked: OR=1.6 (0.8-3.2; 19)	
Hansen (2001a)	Work history	Denmark	Case-control (pop)	7035 cases and controls	All night work: OR=1.5 (1.3-1.7; 434) Employment>6yrs: OR=1.7 (1.3-1.7; 117) Beverage manufacture: OR=1.2 (0.7-1.8; 41) Land transport: OR=1.1 (0.7-1.7; 39) Catering: OR=1.5 (1.2-1.7; 300) Air transport: OR=1.9 (1.6-3.0; 54) Nurses only: RR=1.3 (1.1-1.4)	Age, social class, age at 1st birth, age at last birth, parity/ no. of children
O'Leary *et al*, (2006)	Work history	USA	Case-control (pop)	576 cases/585 controls	Evening or overnight: OR=1.04 (0.79-1.38; 174) Evening only: OR=1.21 (0.9-1.64; 148) Any overnight: OR=0.55 (0.32-0.94; 26) Overnight only: OR=0.64 (0.28-1.45; 10)	Age, parity, education, family history of breast cancer, benign breast disease, BMI; matched by 5-yr age group, stratified by menopausal status

*Rotating night work
‡Two reports of the same cohort
§At least 3 nights per month
†At least 3 nights per week

In a US population-based case-control study, an odds ratio of 1.6 (95% CI 1.0-2.5) was calculated for breast cancer cases who had ever worked the "graveyard" shift in the 10 years prior to diagnosis (i.e. eight hours between 7 pm and 9 am), with a significant positive correlation between increasing risk and shift-work hours per week as well as number of shift-work years worked (Davis *et al,* 2001) (Table 8). The risk increased by number of hours per week on the graveyard shift and by the number of years with at least one graveyard shift per week within the 10-year period. A second US population-based case-control study by O'Leary *et al.* (2006) describes 576 women diagnosed with breast cancer in 1996/97 in two counties on Long Island matched to 585 controls. They found no association between breast cancer and any shift-work (considered to be evenings and overnight work) or any evening work (adjusted OR = 1.04, 95% CI 0.79-1.38 and adjusted OR = 1.08, 95% CI 0.81-1.44 respectively). Evening work only produced a non-significant excess of OR = 1.21 (95% CI 0.9-1.64) but any or only overnight work showed a non-significant deficit of breast cancer of 45-35% (OR = 0.64; 95% CI 0.28-1.45). These associations persisted when age, occupation and period of employment were considered, although more than five years evening work only employment was found to increase risk slightly to OR = 1.24 (95% CI 0.86-1.8). Furthermore, an increasing deficit of risk was identified for increasing duration of overnight shiftwork (less than 8 years: OR=0.74, 95% CI 0.32-1.68; more than 8 years: OR=0.32, 95% CI 0.12-0.83). Despite the study not supporting shift work as a factor in breast cancer risk, O'Leary *et al.* (2006) do identify an elevation associated with non-occupational light-at-night exposure, with an OR = 1.65 (95% CI 1.02-2.69) for women who frequently turned on lights at home during sleep hours.

A recent review by Kolstad (2008) of nightshift work and the risk of cancer evaluated many of the epidemiological studies included in Table 8. Kolstad concluded that three studies reported a significant increase in breast cancer for long-term night-work beyond 20-30 years (Schernhammer *et al,* 2001; 2006; Lie *et al,* 2006). Two further studies indicated an increased breast cancer risk but only considered shorter periods of employment (Hansen 2001a; Davies *et al,* 2001) and another only observed an increased risk for women aged over 50 years (Tynes *et al,* 1996). Negative trends were reported by two studies (O'Leary *et al,* 2006; Schwartbaum *et al,* 2007). Definition of "night-work" varies from study to study and a consistent classification has not yet been developed. Kolstad urges caution, therefore, when comparing the findings of the different epidemiologic studies particularly with regard to the potential for difference between fixed (or permanent) night shifts and non-fixed (or rotating/mixed) and temporary night workers. Cumulative night shifts, which would be expected to be higher for fixed shift workers compared to non-fixed, is one surrogate measure of the potential difference but it has been argued that workers on rotating night shifts, hence fewer cumulative exposures, have the highest cancer risk due to a constantly altering circadian rhythm (Schernhammer *et al,* 2001). Hansen *et al,* (2006), however, note that melatonin concentrations were lower in fixed compared to rotating nightshift workers, conflicting with the hypothesis concerning irregular circadian phases. Adjustment for confounding from principally lifestyle and reproductive factors was generally carried out for most of the studies but the inter-relationship of these factors with nightshift work and the influence of other occupational factors was not known (Kolstad 2008; IEH 2005; Swerdlow 2003). It is possible that female night-workers have different lifestyles to non-night-workers, including increased levels of smoking, alcohol consumption and higher BMIs (Schernhammer *et al,* 2001). Occupational confounders include exposure to EMF and ionising radiation, particularly in medical diagnostics, both of which are explored in subsequent sections (Kliukiene *et al,* 2003). Overall, Kolstad concludes there are indications of a long-term effect but it must be treated with extreme caution as the number of studies is small, positive studies were all conducted for the same occupational group (nurses on nightshift), and the risk estimates only moderately raised, making the results sensitive to bias, including recall bias, chance and confounding.

2.2.2 FLIGHT PERSONNEL

Flight personnel, cabin crew and pilots, are exposed to two potential breast cancer causal factors: night-work/time-zone shift-work and ionising radiation. Other factors that have been cited as agents

or circumstances associated with breast cancer, including engine exhaust gases, jet fuel, ozone, VOCs, EMF, radiofrequency radiation, pesticides, UV radiation, and different lifestyle factors (Blettner *et al,* 1998). Pukkala *et al,* (1995) emphasise occupational exposure to ionising radiation for flight personnel; Mawson (1998), however, suggested that disruption of circadian rhythms (i.e. shift-work) may be more important, an issue further identified by Grajewski *et al,* (2003). Disruption of circadian rhythms (Mawson 1998; Grajewski *et al,* 2003) and ionising radiation are the two most frequently cited occupational causal factors associated with breast cancer incidence in flight personnel; as circadian rhythm disruption resulting in melatonin deficiency has been discussed previously, no further introduction is necessary.

Ionising radiation encompasses a number of particles and photons with sufficient energy to ionise atoms in the human body, hence inducing chemical changes that may have a biological impact on cell function. By far the greatest exposure to ionising radiation is from natural sources such as radon gas or cosmic rays but from the late 19th century, man-made sources have been developed resulting in exposures to ionising radiation during diagnosis of disease and treatment of patients, production/use of nuclear weapons and in the generation of electricity using nuclear reactors (IARC, 2000). Flight personnel can therefore be expected to have one of the highest occupational exposures to ionising radiation derived from natural sources, gamma-radiation and neutrons of extraterrestrial origin often referred to as "cosmic radiation". It has been estimated that an annual effective dose to airline crew will be in the region of 3 mSv (UNSCEAR 1993), although higher levels up to 6 mSv per year have been estimated for flight personnel flying at high altitudes (Blettner *et al,* 2003; Rafnsson *et al,* 2000; Tokumaru *et al,* 2006; UNSCEAR 2008). Radiation dose increases with altitude, with the dose doubling every 1500 m (Pukkala *et al,* 1995). It has been estimated that half the effective dose of ionising radiation at high altitude or at polar regions is due to neutrons rather than gamma rays (Boice *et al,* 2000). It may therefore be expected that short haul flights will lead to lower dose exposure than long haul flights but differences in region also lead to different doses; flights in Canada have been suggested to lead to higher levels of exposure to cosmic radiation than flights within Europe (IARC 2000). Small but repeated dose rates have been shown to be as potentially carcinogenic as large but infrequent doses, showing that the number of years worked is as important as types of flights flown (Pukkala *et al,* 1995). As data on flight profiles are notoriously difficult to obtain because few airline companies record such information, period of employment can be used as a surrogate for exposure. Due to potential confounding by shift-work patterns and possibly electromagnetic radiation, flight personnel are considered separately to other occupations exposed to ionising radiation.

There have been a number of meta-analyses evaluating breast cancer risk in female flight personnel (Table 9). Ballard *et al,* (2000) reported the results of a meta-analysis based on two cohort studies (Pukkala et la. 1995; Wartenberg and Stapleton 1998), with a relative risk for incidence of breast cancer in female flight attendants of 1.35 (95% CI 1.00-1.83). Buja *et al,* (2006) report the findings of a meta-analysis of cancer incidence among female flight attendants based on the findings of seven published studies (Pukkala *et al,* 1995; Rafnsson *et al,* 2001; Haldorsen *et al,* 2001; Linnersjo *et al,* 2003; Reynolds *et al,* 2002; Wartenberg and Stapleton 1998; Lynge 1996), determining a meta-SIR for breast carcinoma of 1.40 (95% posterior interval 1.19-1.65), an almost identical significant risk estimate to that determined by Tokumaru *et al,* (2006) in their meta-analysis (RR = 1.41; 95% CI 1.22-1.62) based on five cohort studies (Pukkala *et al,* 1995; Haldorsen *et al,* 2001; Rafnsson *et al,* 2001; Reynolds *et al,* 2002; Linnersjo *et al,* 2003). The meta-analysis by Megdal *et al,* (2005), using the same studies as Buja *et al,* (2006), report a SIR for breast cancer in flight personnel of 1.44 (95% CI 1.26-1.65); unlike other meta-analyses, Megdal and coworkers assign the risk to circadian disruption, arguing that the similarity between the meta-RR obtained for flight personnel is very similar to the meta-RR obtained for other night work occupations exposed only to background levels of ionising radiation. The slight difference between the Megdal *et al,* (2005) and Buja *et al,* (2006) meta-SIRs is due to the different treatment of the individual risk estimates: Buja *et al.* only use values of two significant figures while Megdal and coworkers use the risk estimates quoted by the individual studies, frequently three significant figures. A more recent meta-analysis by Erren *et al,* (2008) evaluated all 12 of the previously published studies (see Table 9) on flight

personnel and determined a fixed-effect meta-risk for female cabin crew of 1.7 (95% CI 1.4-2.1) for breast cancer. If only European studies are considered, the risk decreases slightly to 1.6 (95% CI 1.2-2.1). Similarly, if only cohort studies are used, a relative risk of 1.6 (95% CI 1.3-2.0) is obtained. Risk of incidence exceeds risk of mortality (SIR only studies = 1.8; 95% CI 1.4-2.3: SMR only studies = 1.2; 95% CI 0.7-1.9), as would be expected by the improvements in medical care achieved over the last few decades. However, where more than one risk estimate is provided by an epidemiologic study, Erren et al (2008) use the estimate which shows the greatest elevation in breast cancer risk. This may be validated by the argument that many of the larger risk estimates correspond to longer flying times or longer distance flights for which exposure to shift-work patterns, ionising radiation and other aeroplane cabin factors would be greatest, and larger periods of employment. However, meta-analyses from Ballard *et al,* (2000), Megdal *et al,* (2005), Buja *et al,* (2006) and Tokumaru *et al,* (2006) use the general SIR values applicable across all potential flight personnel scenarios, unless specified, generating a meta-SIR in the region of 1.4.

The meta-analyses use a combination of the cohort studies described here (Table 9). Blettner *et al,* (2002) reported a SMR for female airline cabin attendants of 1.28 (95% CI 0.72-2.20) and concluded that reproductive risk factors probably contributed more than exposure to ionising radiation due to absence of association with duration of employment. Linnersjo *et al,* (2003) support the supposition of the influence of reproductive history over occupational exposure for a non-significant increase of breast cancer in female flight personnel (SIR = 1.30; 95% CI 0.85-1.74). Ballard *et al,* (2002) provide a SMR of 0.99 (95% CI 0.36-2.15) for a cohort of 3428 female cabin attendants. Reynolds *et al,* (2002) report a female breast cancer incidence over 30% higher than expected in flight personnel, with a SIR of 1.29 (95% CI 0.99-1.66) for non-Hispanic white female flight attendants, rising to a SIR of 1.42 (95% CI 1.09-1.83) for all races combined in the cohort. SIRs for female breast cancer appeared to be higher for those flying international compared to domestic flights, for cohort members with longest occupational tenure (15 years or more) and those who were younger at age of entry (to the union: under 25 years) (Table 9). A cohort of 44,000 airline cabin crew workers from across Europe identified a slight but non-significant association with breast cancer mortality (SMR = 1.11; 95% CI 0.82-1.48); this association was found to increase for long-term employment (SMR = 1.28; 95% CI 0.81-2.02) (Zeeb *et al,* 2003). Pukkala *et al,* (1995) report a significant SIR of 1.87 (95% CI 1.15-2.23) among a cohort of 1577 female flight personnel, with the risk greater for increasing lag time since recruitment and also higher for increased time in exposed work. Pukkala *et al.* (1995) also find that reproductive risk factors (associated with parity, number of children and age at first birth) for breast cancer in the female flight personnel of their cohort were higher compared to the Finnish population generally, and suggest that there may be a multiplicative effect of radiation (or other occupational risk factor) and reproductive risk factors as identified among survivors of the atomic bomb (Land *et al,* 1994a, 1994b). Elevated breast cancer risks associated with cosmic radiation is also suggested by Danish census data which report a SIR of 1.61 (95% CI 0.9-2.7) for female airline cabin attendants (Lynge 1996). An unpublished report by Wartenberg and Stapleton (1998) with a SIR for breast cancer of 2.0 (95% CI 1.0-4.3) has been cited by some of the meta-analyses (Ballard *et al,* 2000; Buja *et al,* 2006; Tokumaru *et al,* 2006). Haldorsen *et al.* (2001) did not observe increased risk of radiation-induced cancers in Norwegian airline cabin crew, with a SIR for female breast cancer of 1.1 (95% CI 0.8-1.5), declining to SIR = 0.9 (95% CI 0.3-2.2) for long service personnel (>15 years). Mortality from breast cancer was not increased for Greek female flight crew, with Paridou *et al,* (2003) reporting a SMR of 1.0 (95% CI 0.1-3.7). Rafnsson *et al.* (2001) report a population-based cohort study of 1690 airline staff, of whom 1532 were women, employed by Icelandic airline companies that considers the confounding effect of reproductive history (parity, number of children, age at first child). Women in the total cohort had increased but borderline significance risk for breast cancer (SIR = 1.5; 95% CI 1.0-2.1). A significant SIR for breast cancer of 1.6 (95% CI 1.0-2.4) with a 15-year lag time was determined, although the risk estimate increased from SIR = 4.1 (95% CI 1.7-8.5) for one or more employment years after a 20-year lag time (i.e. employment after 1971) to SIR = 5.7 (95% CI 1.5-14.6) for eight or more employment years and 20 years lag time. The authors suggest that the causal factors for this increase could be one or a combination of ionising (cosmic) radiation, circadian rhythm disturbance, electromagnetic fields or another

unidentified agent (e.g. VOCs). Wartenberg and Stapleton (1998) report a retrospective cohort survey of retired flight attendants from one US airline with a SIR for breast cancer of 2.0 (95% CI 1.0-4.3); while exposure to ionising radiation is cited as a potential causal factor, use of the pesticide DDT in aircraft cabins prior to takeoff is suggested to be another potential causal agent. The authors report an odds ratio of 2.2 (95% CI 0.4-10.9) for an association between breast cancer and higher than median exposures to DDT and an OR of 0.8 (95% CI 0.2-3.5) for breast cancer and number of flights (as a surrogate for exposure to ionising radiation) (Wartenberg and Stapleton 1998). The association between pesticide use in aircraft cabins and breast cancer incidence is refuted by Auvinen *et al* (1999). Pesticides are considered further in a subsequent section.

A number of nested case-control studies of breast cancer in flight personnel have been reported, some of which have been included in meta-analyses (Erren *et al,* 2008). The results of the study by Kojo *et al,* (2005) found that family history of breast cancer was the strongest determinant of breast cancer (multivariate analysis OR = 5.52; 95% CI 1.44-21.23) in female flight attendants, with a number of other non-occupational factors also showing strong associations. Sleep rhythm disruption was the strongest of the occupational associations with breast cancer (multivariate analysis OR = 1.52; 95% CI 0.49-4.74) while cumulative radiation dose showed negligible effects on breast cancer (multivariate OR = 0.93; 95% CI 0.68-1.27); Kojo *et al.* (2005) conclude that established risk factors are prevalent for female flight personnel. Rafnsson *et al.* (2003) carried out a nested case-control study within a cohort of 1532 female flight personnel, adjusted for reproductive factors, reporting odds ratios of 5.24 (95% CI 1.58-17.38) and 0.82 (95% CI 0.34-1.97) for those employed for five or more years before 1971 and after 1971, respectively, compared to those with less than five years employment in the two time periods. Unlike most of the other studies, this study does consider the potential influence of confounding factors such as reproductive factors and reveals that there is an association between employment as flight personnel and risk of breast cancer. However, an odds ratio that is higher in the pre-jet age (before 1971) suggests that causal factors other than ionising radiation and circadian rhythm disruption dominate, contradicting risk estimates from other studies that identify greater associations in the jet age (1971 onwards) due to ability to fly at higher altitudes and for greater distances (Rafnsson *et al,* 2001). Conversely, higher levels of risk for those employed pre-1971 concur with the long lag time seen in other studies (Pukkala *et al,* 1995).

Reynolds *et al,* (2002) further note that the cumulative dose of ionising radiation may exceed 120mSv over 20 years of work as a flight attendant, which is greater than the cumulative dose of 100mSv reportedly associated with increased risk of leukaemia in nuclear workers (Cardis *et al,* 1995). However, based on studies of acute exposures, the RR of mortality from all cancers after exposure to 1000 mSv has been estimated to be 1.6 (Pierce *et al,* 1996); assuming linearity and no risk reduction, the RR estimate for an exposure to 120 mSv would be 1.07 and hence not detectable by epidemiologic methods (Boice *et al,* 2000). This therefore suggests that other occupational, environmental, reproductive and lifestyle factors contribute to the increased risk of breast cancer among female flight personnel. For flight personnel in particular, shift work, plus the frequent crossing of time zones (Swerdlow 2003) may prove to be of greater importance than exposure to ionising radiation. However, the relative importance of occupational exposures compared to reproductive factors requires further evaluation, with various studies identifying different levels of association (Rafnsson *et al,* 2003; Linnersjo *et al,* 2003). Also, the long latency associated with the developed of these tumours (Table 9) indicates a need for more long-term follow-up.

Table 9: Studies of flight personnel and female breast cancer

Reference	Country	Design	Study size	Results (95% CI)	Adjusted for confounders
Ballard *et al,* (2000)		Meta-analysis	2 studies	FES mRR=1.35 (1.00-1.83) Without SES adj., mRR=1.89 (1.40-2.56)	Socio-economic status (SES)
Megdal *et al,* (2005)		Meta-analysis	7 studies	Meta-SIR=1.44 (1.26-1.65)	
Buja *et al,* (2006)		Meta-analysis	7 studies	Meta-SIR=1.40 (1.19-1.65)	
Tokumaru *et al,* (2006)		Meta-analysis	5 studies	Meta-RR=1.41 (1.22-1.62)	
Erren *et al,* (2008)		Meta-analysis	12 studies	All studies combined: FES=1.7 (1.4-2.1) Europe only: FES=1.6 (1.2-2.1)	
Pukkala *et al,* (1995)	Finland	Cohort	1577	Any employment: SIR=1.87 (1.15-2.23) Employment≥2yrs: SIR=2.0 (1.2-3.2) Employment 10yrs: SIR=2.1 (0.9-3.9) After 15-19 year lag: SIR=3.4 (1.5-6.8) ≥20 yrs lag: SIR=2.1 (1.1-4.0)	Age; parity controlled at group level (cohort vs. reference population)
Lynge (1996)	Denmark	Cohort	915	SIR=1.61 (0.90-2.70)	Age
Wartenberg and Stapleton. (1998)	USA	Cohort	287	SIR=2.0 (1.00-4.3)	Age
Haldorsen *et al,* (2001)	Norway	Cohort	3105	Any employment: SIR=1.1 (0.8-1.5) Employment≥15yrs: SIR=0.9 (0.3-2.2)	Age, no. children, age at 1st birth
Rafnsson *et al,* (2001)	Iceland	Cohort	1532	All: SIR=1.5 (1.00-2.10) After 15yr lag: SIR=1.6 (1.0-2.4) +2yrs employment: SIR=1.7 (no 95% CI given) +8yrs employment: SIR=1.8 (no 95% CI given) +20yrs employment: SIR=1.6(no 95% CI given) +1yr employ. and 20yr lag: SIR=4.1 (1.7-8.5) +2yr employ. and 20yr lag: SIR=4.0 (1.3-9.3) +8yr employ. and 20yr lag: SIR=5.7 (1.5-14.6)	Age, parity, number of children, age at 1st birth
Ballard *et al,* (2002)	Italy	Cohort	3428	SMR=0.99 (0.36-2.15)	

Reference	Country	Design	Study size	Results (95% CI)	Adjusted for confounders
Blettner *et al*, (2002)	Germany	Cohort	16014	SMR=1.28 (0.72-2.20)	Age
Reynolds *et al*, (2002)	USA (California)	Cohort	6895	Any: SIR=1.42 (1.09-1.83) International: SIR=1.79 (1.21-2.54) Employment≥15+yrs: SIR=1.57 (1.16-2.08) Starting age <25yrs: SIR=1.72 (1.23-2.34)	Age
Linnersjo *et al*, (2003)	Sweden	Cohort	2324	Any: SIR=1.30 (0.85-1.74) >5000 flight hours at high altitude, long distance: OR=3.27 (0.54-19.7)	Age; parity controlled at group level (cohort vs. reference population)
Paridou *et al*, (2003)	Greece	Cohort	1835 male and female	SMR=1.0 (0.1-3.7)	
Zeeb *et al*, (2003)	Europe	Cohort	33063	Any: SMR=1.11 (0.82-1.48) 10-<20 yrs working: SMR=1.28 (0.81-2.02) Pre-jet work: SMR=1.27 (0.74-2.07)	Age
Rafnsson *et al*, (2003)	Iceland	Nested case-control	35 cases/140 controls	All ≥5yrs vs. <5yrs: General: OR=2.1 (0.93-4.73) Pre-jet era (to 1970): OR=5.24 (1.58-17.4) Jet era (from 1971): OR=0.82 (0.34-1.97) 20 years lag: OR=3.42 (1.05-11.20) 30 years lag: OR=3.51 (0.75-16.5)	Age at 1st parity, number of children, length of employment
Kojo *et al*, (2005)	Finland	Nested case-control	27 cases/103 controls	Cumulative dose (per 10mSv): OR=0.93 (0.68-1.27) Frequent menstrual cycle disruption: OR=0.56 (0.12-2.61) Frequent sleep rhythm disruption: OR=1.52 (0.49-4.74)	No. of births, age at 1st birth, breast feeding, no. of abortions (spontaneous and induced), age at menarche, age at menopause, oral contraceptives, mammography screening, HRT, family history of breast cancer, benign breast disease, alcohol/smoking status

2.2.3 OTHER EXPOSURES

Ionising radiation except flight personnel

For occupational exposures, the main routes of exposure involving radiation or radioactive sources are external to the body and range from 0.1 - 6 mSv per year with an estimated annual collective dose of 4300 person-Sv and a background level of 2.4 mSv per year. Miners and flight personnel are exposed to natural sources of ionising radiation, radon and cosmic radiation. It has been estimated that an annual effective dose for miners can be as high as 6 mSv; flight personnel are discussed in Section 2.2.2 above (UNSCEAR 1993). The predominant exposure to man-made radiation is through medical applications, particularly the use of X-rays as well as γ-, β-rays and radiopharmaceuticals, and an average annual effective occupational dose has been estimated to be 0.5 mSv; higher doses can be expected from exposures in the early parts of 20th century when occupational safety requirements were less rigorous (UNSCEAR 1993). For nuclear power plant workers, exposure to γ-radiation has resulted in average annual effective doses of 2.9 mSv for monitored workers employed between 1985 and 1989 (UNSCEAR 1993); higher levels have been recorded for US nuclear power workers and in remedial situations such as the Chernobyl clean-up (IARC 2000). Industrial uses of γ-radiation and neutrons in the radiography of welded joints, sterilisation of products/food, and during oil well construction result in annual average doses of around 1 mSv whilst military exposures have historically been much higher (IARC 2000). Internal exposures through ingestion/injection of iodine-131 and radium-224 have also been associated with increased risk of breast cancer (UNSCEAR 2000).

IARC (2000) have identified a number of populations showing correlations between receipt of heavy exposures to ionising radiation and breast cancer. A statistically significant correlation was found between breast cancer and atomic bomb survivors (excess relative risk (ERR) = 1.6, 95% CI 1.1-2.2; Tokunaga *et al,* 1994; Thompson *et al,* 1994), treatment for benign breast disease (relative risk (RR) = 3.6, 95% CI 2.8-4.6; Mattsson *et al.* 1993 and RR = 3.2, 90% CI 2.3-4.3; Shore *et al,* 1986) and fluoroscopy of the chest (standardised mortality ratio (SMR) = 1.5, 95% CI 1.3-1.6; Howe and McLaughlin 1996). Exposure of premenopausal women to ionising radiation, such as atomic bomb explosions or medical treatments involving X-rays, is closely associated with breast cancer risks; exposure after age 40 years or post-menopausal exposure tend not to correlate with breast cancer risk (UNSCEAR 2008; IARC 2000; Carpenter *et al,* 1994). The UNSCEAR Reports conclude that there is compelling evidence for effects of ionising radiation exposure on breast cancer rates, with a linear dose response widely reported (UNSCEAR 2008, 2000). Age of exposure appears to be a key factor although confounding from other known breast cancer risk factors has not been assessed; radiation may act additively or even multiplicatively with certain of these risk factors (Ronckers *et al,* 2005; UNSCEAR 2008). A recent report on male breast cancer in survivors of atomic bombings noted a statistically significant increase in the risk with increasing dose although only a small number of cases were found (Ron *et al,* 2005).

Chobanova *et al.* (2007) report that breast cancer incidence was more frequently diagnosed in medical radiation workers than other cancer types but no effects of dose or duration were found. Doody *et al,* (2000) assessed the mortality of Catholic nuns employed as radiologists and reported a 10% deficit of breast cancer risk (SMR= 0.9; 95% CI 0.6-1.3) compared to other radiologists. Notably, nuns generally experienced a 20% excess of breast cancer compared to other US females (SMR=1.2; 95% CI 0.8-1.7), suggesting that the study requires re-analysis. Jartti *et al,* (2006) identified a slightly elevated risk of breast cancer among physicians occupationally exposed to ionising radiation in Finland compared to other physicians (RR = 1.7; 95% CI 1.0-3.1). Mohan *et al,* (2003) evaluated cancer risks resulting from exposure to low-dose ionising radiation in a cohort of 146,022 US radiologic technologists (73% women) and found an elevated risk for breast cancer (RR = 2.92; 95% CI 1.22-7.00) among workers employed prior to 1940 compared to those first employed after 1960. Risks declined with more recent year of first employment irrespective of employment duration but increased with increasing duration of employment prior to 1950, a result supported by Wang *et al,* (1996; 2002) who report on a Chinese cohort of female medical

diagnostic X-ray workers (RR = 1.2; no 95% CI provided). The elevated mortality risks for breast cancer are consistent with greater occupational exposures to ionising radiation prior to 1950 than in more recent times. A similar study of a slightly smaller cohort of US radiologists reported a SIR of 1.16 (95% CI 1.09-1.23) for female breast cancer (Sigurdson *et al,* 2003) while Doody *et al.* (1998) found significant risks of female breast cancer were correlated with employment prior to 1940 (SMR=1.5; 95% CI 1.2-1.9) and among women certified as radiological technicians for more than 30 years (SMR = 1.4; 95% CI 1.2-1.7) in a cohort of 143,517 radiologists certified between 1926 and 1980. However, it must be noted that the SMR for breast cancer in the Doody *et al,* (1998) paper, as compared to the general population, was 0.99 and only became significantly elevated relative to all other cancers in a test of homogeneity (ratio of SMRs = 1.3). Earlier nested case-control studies from a cohort of female radiologists from the American Registry of Radiologic Technicians did not find an occupational association with breast cancer, with more than 50% of reported breast cancers explained by established risk factors such as age at menarche, parity, family history, prior breast disease and alcohol consumption (Boice *et al,* 1995; Doody *et al,* 1995). However, a slightly elevated RR of 1.13 (95% CI 0.79-1.64) was found for women employed as radiologists for more than 20 years. The joint effects of exposure to ionising radiation and genetic variation on breast cancer incidence were evaluated in US radiologic technologists, finding effect modification of the radiation and breast cancer dose-response relationship (Sigurdson *et al,* 2007). Smith and Doll (1981) do not report risk estimates for breast cancer among British radiologists who had joined the British radiological society between 1897 and 1954, supporting the more recent assertion that the more rigorous health and safety regulations introduced since the 1940s have considerably reduced exposures (Doody *et al,* 2006).

A cohort of 58,320 workers employed at the French Atomic Energy Commission between 1946 and 1994 generally revealed the "healthy worker effect" in both men and women, although a borderline significant excess of female breast cancer was recorded, with a SMR of 1.14 (95% CI 0.94-1.37) (Telle-Lamberton *et al,* 2004). Goldberg and Labreche (1996) found little support for an association between nuclear industry workers and breast cancer incidence in a large meta-analysis. Occupational exposure of female radium-dial painters and aircraft personnel have been found to correlate with breast cancer but the level of significance does vary (Adams and Brues 1980; Stebbings *et al,* 1984; Baverstock *et al,* 1981; Schneider and Burkart 1998). There are a large number of confounding factors, not least the influence of natural sources of ionising radiation and reproductive history of the women in the cohorts.

Thus, it can be concluded that there may be a small risk from long-term employment in medical diagnostics but established risk factors associated with reproductive history, genetics and lifestyle factors frequently confound the results. During the early nuclear years, high levels of exposure were recorded for a large number of workers in medical diagnostics, nuclear power industry and in the military; more recent exposures can be considered to be much lower due to the recognition of the long-term health effects wrought and the introduction of health and safety precautions.

Electromagnetic fields (non-ionising radiation)

While epidemiological studies have suggested a link between occupational and environmental exposure to electromagnetic fields (EMFs) and cancer, with an IARC classification for low-frequency EMFs of "possibly carcinogenic to humans" (Group 2B), this does not apply to breast cancer for which the evidence is considered to be inadequate (IARC 2002). There exist a number of reports that appear to demonstrate an excess of female breast cancer due to occupational exposure to EMF (e.g. Coogan *et al,* 1996; Kliukiene *et al,* 1999; Forssen *et al,* 2000; Van Wijngaarden *et al,* 2001; McElroy *et al,* 2007), balanced by an almost equal number of studies that do not identify any association between breast cancer risk and EMF exposure (e.g. Vagero and Olin 1983; Vagero *et al,* 1985; Guenel *et al,* 1993; Johansen and Olsen 1998; Forssen *et al,* 2005).

One of the first reports of an association between occupational exposure to EMF and female breast cancer was published in 1994 (Loomis *et al,* 1994) and followed on from the paper by Stevens

(1987) which proposed a melatonin secretion mechanism through which EMF might influence hormone-related cancers such as breast cancer, a mechanism later suggested to explain the association between night-work and female breast cancer (see section above). Loomis *et al,* (1994) reported an elevated relative risk of 1.38 (95% CI1.0-1.8) for women employed in electrical occupations but a risk deficit for all other occupations with potential for exposure. Blettner and Schlehofer (1999) reviewed epidemiologic studies published between 1980 and 1997 investigating risk factors in people exposed to high frequency electromagnetic fields (HF-EMF), concluding that the relative risks for breast cancer were small, non-significant and inconsistent. Erren (2001) also evaluated a number of EMF studies and, while identifying elevated relative risks for breast cancer in both women and men, the results of the studies included in the meta-analysis were very variable and, in part, contradictory. Nevertheless, a significant pooled RR from the studies in women was reported to be 1.12 (95% CI 1.09-1.15). Feychting *et al.* (2005) report that EMFs do not appear to be a risk factor for breast cancer and that there has been insufficient work evaluating the risks of radio frequency fields. Schreiber *et al,* (1993) did not find any association between exposure to extremely low frequency electromagnetic fields and breast cancer incidence as did the study reported by Caplan *et al,* (2000). Floderus *et al,* (1999) report a slight elevation in risk in women occupationally exposed to medium and high electromagnetic levels (RR_{med} = 1.2, 95% CI 1.2-1.3; RR_{high} = 1.1, 95% CI 1.0-1.1), while Labreche *et al,* (2003) found a small increase in breast cancer risk among women in occupations exposed to low-frequency EMFs. Kliukiene *et al,* (2003) report the findings of a follow-up study involving a cohort of Norwegian female radio and telegraph operators for the period 1961 and 2002; a SIR for breast cancer of 1.30 (95% CI 1.05-1.58) was calculated (Table 8), with higher odds ratios in the nested case-control study for groups with the highest cumulative exposure to extremely low frequency (around 50 Hz) and radio frequency (450 kHz-25 MHz) fields (OR = 1.78; 95% CI 0.59-5.41). Elevated risks were found in both pre- and postmenopausal women (OR = 1.41; 95% CI 0.54-3.69 for both) but inclusion of lag times did not contribute any additional explanation. This Norwegian study included shift-workers employed for night-time and time-zone work but does not consider shift-work further. An earlier report for the same cohort by Tynes *et al.* (1996) did evaluate shift-work and is discussed in the appropriate section above. Residential exposure does not appear to be a causal factor (Davis *et al,* 2002). There is inconsistent evidence for a dose-response effect of EMF and breast cancer risk as well as potential confounding from light-at-night/shift-work (Kheifets *et al,* 1999).

Reports of associations between EMF exposure and male breast cancer have also been published. In fact, some of the first reports of an excess risk of breast cancer arose from studies of male electrical workers exposed to EMF (Tynes and Andersen 1990; Demers *et al,* 1991; Matanoski *et al,* 1991; Pollan *et al,* 2001) although a study reported by Theriault *et al,* (1994) did not find an association (numbers too small for suitable analysis). A cluster of 3 male breast cancer cases were observed in a group of 200 men who worked in the basement office of a building, adjacent to an electrical switch-gear room which generated high magnetic fields (Milham 2004). With 0.03 expected cases, an increased risk of about 100-fold supports other epidemiologic studies, including Erren *et al,* (2001) who reported a RR = 1.37 (95% CI 1.11-1.71), suggesting an association between male breast cancer and electromagnetic fields that requires further evaluation.

Ethylene oxide

Ethylene oxide is used as a sterilising agent or intermediary in the chemical synthesis of ethylene glycol, non-ionic surfactants and other derivatives in smaller quantities. It is recognised from animal studies to be a potent genotoxin and animal carcinogen, causing mammary tumours in mice, but epidemiologic evidence of a carcinogenic effect in humans is limited. It has been classified by IARC as carcinogenic to humans (Group 1) based primarily upon sufficient evidence in animals and genotoxic considerations (IARC, 1994; Grosse *et al,* 2007). A series of reports by Hogstedt and colleagues (Hogstedt *et al,*, 1986; Hogstedt *et al,*, 1979a, 1979b) raised concern about the health risk of a cluster of ethylene oxide exposed workers. Since then there have been studies varying in size and quality in several countries. No clear association between ethylene oxide exposure and any cancer has been observed (Blair and Kazerouni, 1997). A meta-analysis by Shore et al (1993) found

no excesses of any cancer. This meta-analysis of the findings from 10 cohort studies from five countries, including 33,000 workers and over 800 cancers was updated by Teta *et al.* (1999) with similar results of no excess, and no trend with duration or intensity of exposure or latency; leukaemia was the only cancer with an, albeit non-significant, excess (SMR = 1.08; 95% CI 0.61-1.93). In a study of 2,876 British workers exposed to ethylene oxide, Coggon et al (2004) found that mortality was below expectation for breast cancer (11 deaths versus 13.2 expected; SMR = 0.84, 95% CI 0.42-1.51) as well as close to or below expectation for all cancers, indicating the possible capacity of human cells to repair DNA damage caused by ethylene oxide.

Steenland *et al.* (2004) report mortality in an extended follow-up study of a cohort of 18,235 men and women exposed to ethylene oxide; whilst female breast cancer did not show an overall excess (SMR = 0.99; 95% CI 0.81-1.2), after a 20 year lag, an excess in the highest cumulative exposure group was revealed indicative of a positive exposure-response for breast cancer mortality (SMR = 2.07; 95% CI 1.1-3.54). Male breast cancer mortality indicated a non-significant excess, with an SMR of 2.04 (95% CI 0.05-11.37). Earlier work by Steenland *et al.* (2003) found an excess of female breast cancer in a cohort of 7,576 women employed in sterilisation facilities. The excess was observable after a 15-year lag and increasing with increasing exposure; the top quintile of cumulative exposure provided a SIR of 1.27 (95% CI 0.94-1.69). Nevertheless, evidence of occupational exposures affecting breast cancer risk has not been consistent (Snedeker *et al.* 2006).

Other agents

Hansen (2001a) identifies chlorinated hydrocarbon pesticides, organic solvents, and polychlorinated biphenyls (PCBs) as having been associated with breast cancer in various studies (Welp *et al,* 1998; Colborn *et al,* 1993; Hansen 1999). In a review of epidemiological studies, Brody *et al.* (2007) found associations between breast cancer and exposure to polycyclic aromatic hydrocarbons (PAHs), PCBs and organic solvents but report a lack of evidence supporting associations with organochlorine pesticides and dioxins (no meta-analysis). The findings of the review by Salehi *et al.* (2008) also emphasise the potential association between PCBs and PAHs with breast cancer but the lack of evidence for a link between breast cancer and pesticide exposure (no RRs provided). Many of these agents have been described as endocrine disrupters which act as tumour promoters rather than mutagenic or genotoxic tumour initiators (Coyle 2004).

Generally, as the conflicting conclusions from Hansen (2001a) and Brody *et al,* (2007) reveal, the findings of studies assessing associations between pesticide exposure and female breast cancer are ambiguous. For example, one study reports a deficit in SIR of 0.87 (95% CI 074-1.02) for women who ever applied pesticides but a modest elevation based on proximity of home to pesticide application area (Engel *et al,* 2005; Fleming *et al,* 1999(b)). Female breast cancer was found to be significantly elevated in women whose husbands were exposed to the chlorinated pesticides dieldrin (RR=2.0), chlordane (RR=1.7), aldrin (RR=1.9) and lindane (RR=1.7) but not if used by the women themselves (Engel *et al,* 2005). Schecter *et al.* (1997) reports a lack of association between the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT) and breast cancer incidence but more recent work suggests that exposure to DDT before puberty increases the risk of breast cancer, particularly if the exposed women are followed up to their 50s (Cohn *et al,* 2007; Brody *et al,* 2007). The highest DDT exposure category, as evidenced by high levels of the main DDT metabolite dichlorodiphenyldichloroethane (DDE) in human tissues, has been associated with a five-fold increase in risk of breast cancer (Cohn *et al,* 2007). A review by Salehi *et al,* (2008) does not find sufficient epidemiologic evidence to support an association between DDT and breast cancer and there are a large number of studies finding no association (Coyle 2004). Other pesticides that have been associated with breast cancer risk, either through a woman's own use or via their partners, include 2,4,5-trichlorophenoxypropioic acid (2,4,5-TP), captan, chlorpyrifos, dichlorvos, terbufos, heptachlor, diazinon and malathion; occupational and residential use of pesticides have both been identified as potential breast cancer risk factors (Clapp *et al,* 2008). Many pesticides, alongside other widely used substances, have been described as exerting a hormonally active influence. However, female farmers do not show elevated risk of breast cancer (Brody and Rudel

2003). Overall, there are few epidemiological studies assessing the relationship between breast cancer risk and pesticide use/exposure (Salehi *et al,* 2008). Furthermore, the findings of an evaluation by the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) reported that there is no evidence of an association between breast cancer and exposure to DDT, lindane and hexachlorocyclohexane organochlorine pesticides and, although data are limiting, there does not appear to be a link between dieldrin exposure and breast cancer (COC 2003).

Exposure to high levels of dioxins has been associated with elevated levels of breast cancer (Warner *et al,* 2002). However, Brody *et al,* (2007) conclude in a review of epidemiological studies that evidence of an association between dioxin exposure and breast cancer is inconclusive. This same review does suggest that there is a considerable correlation between PCBs and breast cancer but only for women with certain genetic traits. Hence, while the evidence of an association between breast cancer and PCBs is often ambiguous, there appears to be a link between women with a polymorphism in the CYP1A1 gene and greater risk of breast cancer after exposure to PCBs, particularly if post-menopausal (Clapp *et al,* 2008; Brody *et al,* 2007). Salehi *et al,* (2008) find limited evidence of a role for PCBs in the aetiology of breast cancer and Coyle suggests that while PCBs, along with DDT and atrazine, may have been demonstrated to affect tumour growth in rats, the evidence for humans does not yet indicate a causal relationship.

A 48% increased risk of breast cancer has been reported for women enlisted in the US army and occupationally exposed to polycyclic aromatic hydrocarbons (PAHs) through employment as mechanics and transport operatives (Rennix *et al,* 2005). Brody *et al,* (2007) also report an association between breast cancers and PAH exposures, which are frequently associated with vehicle exhausts. As for PCBs, it would seem that certain genetic polymorphisms are at higher risk from PAH exposure than others (Brody *et al,* 2007). Salehi *et al,* (2008) further emphasise PAHs as potential causal factors for breast cancer but as a consequence of environmental rather than only occupational exposure.

High levels of breast cancer incidence in nurses have been widely reported in Europe; whilst shift-working patterns may provide one explanation, there are a number of other agents to which healthcare staff may be exposed, from cytotoxic and cytostatic drugs to formaldehyde and benzene (Snedeker 2006). Xenoestrogens, including alkylphenols and phthalates, are also currently under evaluation as potential breast cancer causal factors (DeBruin and Josephy 2002).

Blair *et al,* (1998) report a non-significant excess of breast cancer in a cohort of 14,457 aircraft maintenance workers exposed to trichloroethylene (RR = 1.8) and various other organic solvents. Exposure to chlorinated organic solvents has not been associated with an elevated SMR for breast cancer (Chang *et al,* 2003a) but has been associated with a significantly elevated proportionate cancer morbidity ratio (PCMR) for breast cancer (Chang *et al,* 2003b). Brody *et al,* (2007) evaluate a number of epidemiological studies investigating occupational exposure to organic solvents and breast cancer. While many of the studies find a positive correlation between exposure and breast cancer incidence, Brody *et al,* (2007) find a number of limitations to the studies that prevent conclusion from being drawn. Not least is the difficulty in separating exposure to different solvents (e.g. methylene chloride, toluene, formaldehyde and carbon tetrachloride). Coyle (2004), however, discusses a number of epidemiological studies that indicate a positive assoaciation between organic solvent exposure and breast cancer risk. Labrech and Goldberg (1997) report that the organic solvents benzene, 1,1-dichloroethane, 1,2-dichloroethane, 1,2-dichloropropane and dichloromethane are all rodent mammary carcinogens. Occupational exposures to benzidine or β–naphthylamine are reported to double the risk of breast cancer (Bulbulyan *et al,* 1995).

Animal cancer bioassays have lead to the identification of more than 42 chemicals with mammary carcinogenic properties (Bennett and Davis 2002; Dunnick *et al,* 1995), although Rudel *et al,* (2007) identify a total of 216 potential mammary carcinogens in animals and 250 oestrogen mimics based on *in vitro* assays. These chemicals include dyes and dye intermediates, some flame

retardants, lead scavengers in gasoline, certain pharmaceutical agents and chemicals used in the manufacture of rubber and polyurethane foams. Low concentrations of cadmium and other heavy metals have been described as oestrogen mimics in rats and have been associated with mammary-gland effects in rats (Coyle 2004); a recent epidemiologic study indicated that exposure to cadmium increases the risk of female breast cancer (McElroy *et al,* 2006). The results of animal developmental toxicity studies have indicated that maternal exposure during pregnancy to substances such as atrazine and bisphenol A may affect cell differentiation and increase the susceptibility of female offspring to breast cancer (Birnbaum and Fenton 2003).

Other circumstances

Camp *et al.* (2003) report significantly increased risk of breast cancer for women in employed in the textile industry in Shanghai; it is not clear whether shift-work has been a confounding factor in the analysis. Similarly, Kuzmickiene *et al.* (2002) report an elevation of breast cancer risk (SIR=1.49; 95% CI 1.08-2.0) among textile processors (spinning/weaving) in a large cotton-manufacturing factory in Lithuania. Ray *et al,* (2007) do not identify elevated levels of breast cancer in female textile workers in Shanghai.

The highest SIRs and SMRs for breast cancer in Denmark and in Scandinavia generally have been reported for female academics (SIR = 1.39, SMR = 1.29) and women married to academics (SIR = 1.21, SMR = 1.16), indicating that the risk factor may be associated with lifestyle rather than occupation (i.e. age at first birth, etc.) (Dano *et al,* 2003; Andersen *et al,* 1999). Incidentally, risks of breast cancer incidence/mortality were lowest for women in agriculture and women married to men working in agriculture (SIR = 0.77, SMR = 0.75; SIR = 0.79, SMR = 0.79 respectively). A number of studies report high levels of breast cancer incidence among teachers although reproductive and lifestyle issues are more likely to be causal factors than occupation (Snedeker 2006).

Goldberg and Labreche (1996) state in a review of 115 epidemiologic studies of occupational risk factors for breast cancer that weak associations have been identified for employment in the pharmaceutical industry and as chemists, hairdressers or beauticians, and occupations involving exposure to very low frequency electromagnetic fields. Little support was found for elevated risks among textile workers, dry cleaning workers and nuclear workers. Ji *et al,* (2008) identified several occupations associated with elevated breast cancer incidence, including technicians in engineering/agriculture/forestry, teaching personnel, textile workers, medical and healthcare workers, administrative occupations, and telecommunications workers, leading to the suggestion that white-collar professionals and some production occupations are associated with an increased risk of breast cancer. Studies have also identified elevated risks from female breast cancer among civilian employees at a US air force base (Mundt *et al,* 2002), UK semiconductor workers (Nichols and Sorahan 2005), Spanish paper and pulp industry workers (Sala-Serra *et al,* 1996), research and biomedical laboratory workers (Shaham *et al,* 2003; Wennborg *et al,* 1999) but lifestyle factors were generally not considered as confounding factors. Many occupational studies, including the study of physicians by Innos *et al* (2002), find that lifestyle factors dominate over occupational risk factors and these are especially relevant for white-collar professionals. It appears that production workers are most affected by occupational risk factors for breast cancer. Possible additive linkages exist between reproductive history and chemical exposures affecting breast cancer, as the high rates found among unmarried female chemists reveals (Walrath *et al,* 1985).

Kruk and Aboul-Enein (2003) report that the breast cancer risk is 29% higher in women with sedentary jobs than those with light or medium physical activity, an association that is particularly relevant to older women (more than 55 years). A small increased risk has also been reported among women in full-time employment who experience work-related stress compared to part-timers (Kuper *et al,* 2007). Marshall *et al,* (1999) identified socioeconomic status as a confounding factor in occupational exposure scenarios for breast cancer while other studies found an association between decreasing physical activity, increasing socioeconomic status and increasing breast cancer

risk particularly in older age groups and potentially associated further with body mass index (Moradi *et al,* 2002; 1999; Rintala *et al,* 2002). Physical activity may be one of the factors that can explain breast cancer deficits in female farmers (Wiklund and Dich 1994).

While male breast cancer is not considered in detail in this report, it should be noted that there are reports of occupational associations with disease incidence. Forastiere *et al,* (1994) report an excess of male breast cancer in urban/traffic policemen (SMR=14.36) indicative of a possible link between motor vehicle exhausts and male breast cancer. Ma *et al,* (2005) report an excess of male breast cancer among fire-fighters (SMR = 7.41; 95% CI 1.99-18.96) but found female fire-fighters had similar cancer mortality patterns to non-fire-fighters. This suggests a similar association as that identified between fire-fighters and prostate cancer and, as suggested earlier, a different aetiology to female breast cancer.

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

The substances/exposures considered in the estimation of the attributable fraction (AF) for breast cancer are those outlined in Table 10. Other substances/exposures not considered specifically by IARC, namely flight attendants, have also been considered in the estimation of AF due to the weight of evidence available.

Table 10: Substances considered in the estimation of the attributable fraction for breast cancer (Group 1 and 2A carcinogens only)

Agents, mixture, circumstance	AF calculation	Strength of evidence	Comments
Group 1: carcinogenic to humans			
Agents, groups of agents			
None specified			
Exposure circumstances			
None specified			
Group 2A: probably carcinogenic to humans			
Agents, groups of agents			
None specified			
Exposure circumstances			
Shift-work	Yes	Suggestive	Flight attendants also evaluated by IARC. Estimation carried out for women only

Data Relevant to the Calculation of AF

The two data elements required are an estimate of relative risk (RR), and either (1) an estimate of the proportion of the population exposed (Pr(E)) from independent data for Great Britain, or (2) an estimate of the proportion of cases exposed (Pr(E|D)) from population based study data.

The RR chosen from a 'best study' source is described for each exposure, with justification of its suitability. Information on the 'best study' and independent data sources for the proportion of the population exposed are also summarised for each exposure in the appropriate section below. In the absence of more precise knowledge of cancer latency, for solid tumours a latency of up to 50 years and at least 10 years has been assumed for all types of the cancer. Therefore it is assumed that exposure at any time between 1956 and 1995 (the Risk Exposure Period, REP) can result in a cancer being recorded in 2005 as an underlying cause of death. Although strictly speaking the REP for cancer registrations recorded in 2004, the year for which estimation has been carried out, would be 1955-1994, for simplification the years 1956 to 1995 have also been used, as for deaths, as the proportion exposed will not be affected. For an independent estimate of the proportion of the population exposed, numbers of workers ever exposed during this period are counted using a point estimate of exposed workers taken from the period. If this is from CAREX relating to 1990-93, an adjustment is made to take account of gross changes in employment levels which have occurred particularly in manufacturing industry and the service sector across the REP. Otherwise a point estimate that represents numbers employed as close as possible to about 35 years before the target year of 2005 is used, as this is thought to represent a 'peak' latency for the solid tumours, and is also close to the mid-point of the REP for estimating numbers ever exposed across the period (for which a linear change in employment levels is implicitly assumed). Where the Census of Employment is used, the point estimate data are for 1971. Where the LFS is used, the first year

available and therefore used is 1979. For shift work, data for 1992 have been used as a point estimate and the 'all industry CAREX' adjustment factor of 0.9 is used to reflect the lower numbers of women employed earlier in the REP. A turnover factor is applied to estimate numbers ever exposed during the REP, determined mainly by the estimate of staff turnover per year during the period. For each exposure therefore, if an AF has been based on independent estimates of numbers exposed, the table of results includes the point estimate of numbers employed, the adjustment factor for CAREX if applicable, the staff turnover estimate, and the resulting estimate of numbers ever exposed during the REP. Other estimates used in the calculations that remain constant across exposures (unless otherwise stated) are given below:

- Number of years in REP = 40

- Proportion in the workplace ever exposed is set to one, i.e. all are assumed to be exposed, in the absence of more detailed information. Where sources other than CAREX are used for the point estimate of numbers exposed, such as the LFS or Census of Employment, a precise as possible definition of workers exposed is sought.

- Numbers ever of working age during the target REP = 19.4 million men, 21.0 million women. This is the denominator for the proportion of the population exposed, and is based on population estimates by age cohort in the target year.

- Total deaths from breast cancer, Great Britain, 2005 = 12,182 for women aged 25+ (11,038 in England and Wales, 1144 in Scotland)

- Total registrations for breast cancer, Great Britain, 2004 = 43,202 for women aged 25+ (36,919 in England, 2366 Wales, 3917 in Scotland). 2004 is the most recent year for which data are available.

Attributable numbers are estimated by multiplying the AF by the total number of cancers in GB. Only cancers which could have been initiated during the risk exposure period are counted, taking normal retirement age into account. Therefore for solid tumour cancers, total deaths or registrations recorded at all adult ages (25+) are used to estimate attributable numbers, and for short latency cancers, deaths and registrations for ages 15-84 for men and 15-79 for women are used.

For each agent where data on worker numbers are only available for men and women combined (CAREX data), the assumed percentage of men is given in addition to the numbers exposed. The allocation to high and low, and occasionally negligible, exposure level categories, or division into separate exposure scenarios, is also included in these tables. Where no separate estimate of relative risk is available for the low exposure level category, an estimate is based on an average of the high/low ratios for cancer-exposure pairs for which data were available.

Full details of the derivation of the above factors and the methods of calculating AF are published separately. Unless otherwise stated, Levin's method is used for estimates using independent estimates of numbers exposed, and Miettinen's method is used for study based estimates. A summary of the methodology is given in the Statistical Appendix.

3.2 SHIFT WORK

(a) Risk estimate:

IARC classify shift work that involves circadian disruption as probably carcinogenic to humans (Group 2A); hence, only shift work that includes night-work need be considered. As definition of "shift-work" and particularly "night-work", exposure types and duration are rarely consistent; it is therefore very difficult to compare the studies and to determine what, if any, circadian disruption has occurred. The majority of studies evaluating the association between breast cancer and shift work, particularly night work, report a wide spectrum of risk estimates, from risk deficits to more than two-fold elevations in risk (Tynes *et al,* 1996; Davis *et al,* 2001; Hansen 2001a; Lie *et al,* 2006; O'Leary *et al,* 2006; Schernhammer *et al,* 2001, 2006; Schwartzbaum *et al,* 2007). Many of the studies do adjust for confounders particularly lifestyle and reproductive factors such as parity, age at menarche, menopausal status, use of the contraceptive pill/HRT, smoking and alcohol consumption but provide inadequate definitions of the type of shift-work considered. Frequently, shift-work has been evaluated after the fact and not as the focus of the study (e.g. Tynes *et al,* 1996). Of the cohort studies, Schernhammer *et al.* (2001; 2006) reports on two large cohorts of US nurses while Schwartzbaum *et al.* (2007) exclude nurses in their census-based study.

Two meta-analysis of studies that exclude flight personnel and have adjusted for reproductive and other risk factors provide broadly similar overall risk estimates of 1.51 (95% CI 1.36-1.68) (Megdal *et al,* 2005) and 1.4 (95% CI 1.3-1.6) (Erren *et al,* 2008). Both meta-analyses use risk estimates for the longest employment and greatest lag time. Megdal *et al.* (2005) uses 6 studies (Tynes *et al,* 1996; Davis *et al,* 2001; Hansen 2001a; Lie *et al,* 2006; Schernhammer *et al,* 2001, 2006). Erren *et al.* (2008) use the same studies plus one further study, which reports a deficit of risk (O'Leary *et al,* 2006). However, there are a number of apparent inaccuracies in the figures used by Erren *et al.* (2008) in their meta-analysis compared to the studies from which they are drawn and hence, despite using fewer studies, the Megdal *et al.* (2005) metaRR is thought to be more accurate. Neither Erren *et al.* (2008) nor Megdal *et al.* (2005) includes the Schwartzbaum *et al.* (2007) study, which also reveals a deficit and therefore may be expected to reduce the meta-risk estimate further. However, Schwartzbaum *et al.* suggest that a key factor for the divergence of their results from other findings is the definitions of exposure and exposure duration used and the scale of the study.

Both meta-analyses note that long periods of night-work employment, lag times and increased incidence in those over 50 years or exposed before age 30 affect the risk of breast cancer; the highest risk estimates from each of the cohort and case-control studies corresponded to these factors and were used in both meta-analyses to derive meta-RRs. The meta-analyses are therefore applicable for 'high' exposure scenarios ie., night shift work. Given the problems with the study by Erren *et al.* (2008) highlighted above, the overall risk estimates of 1.51 (95% CI 1.36-1.68) from Megdal *et al.* (2005) has been used for night shift workers.

(b) Numbers exposed:

There are more than 3.5 million employed as shift workers in the UK (HSE website). Across the European Union, the incidence of shift work is similar for women and men, suggesting a roughly equal division of labour between the sexes in the UK (European Foundation for the Improvement of Living and Working Conditions), although the number of women reporting shift work in the UK has increased since 1993 and continues to rise (McOrmond 2004). However, in Europe, more men than women work night shifts. Similarly, men predominate in permanent shift work posts as opposed to part-time or temporary work taken by female shift workers, with the exception of nursing (McOrmond 2004). IEH (2005) report that just over 5% of the adult (15 years and older) female population in Great Britain is exposed to shift-work (Table 11). McOrmond (2004) cites a slightly higher proportion. In the 16-24 age group, one in five women report doing shift work most of the time in 2003 (McOrmond 2004). Not all of the shift work categories include night-work; based on night-work categories in Table 11, 654,076 women are employed as night shift workers,

36% of total female shift workers. Not all of these women will be exposed to regular patterns of night-work and 154,400 have been described as being employed on night shifts only (24% of all shift work including night-work only and 9% of total day/night shift work).

In 2003, women shift workers were more likely to be employed in the transport and communication industry, accounting for 19% of female workers in this industry (McOrmond 2004). About 17% of women working in public administration, education and health were described as shift workers, compared to 15% in distribution, hotels and restaurants, 11% in other services, 10% in manufacturing and less than 5% in banking, finance, insurance and similar. However, many of these (approximately 30%) will be day workers employed on two-shift systems. The number and pattern of shift work has altered in recent years and it is has been reported that current numbers of night workers are likely to be the highest in recent post-war years reflecting the development of the 24/7 economy (McOrmond 2004). Table 12 shows the increase in number of women shift workers since 1992, with the years 1992-2001 showing the greatest proportional increase (EUStats 2008). Between 1992 and 2007, the number of women shift workers almost doubled. No data are available before 1992, the date when shift work was first included in the Labour Force Survey (LFS).

While the total number of female shift workers listed in Table 12 is slightly higher than the number in Table 11 (2.05 million compared to 1.8 million), the numbers are of similar magnitude. Using the proportion of night workers to shift workers obtained from Table 11 (31%) and assuming that this proportion is consistent over time, it can be estimated that there were 400,611 women night workers in 1992 using total women shift work numbers for that year (Table 12). It can be surmised that levels prior to 1992 were perhaps lower reflecting the decline of manufacturing and production in the UK; however, it is possible that there were more shift workers immediately after the Second World War and this only gradually declined with increasing mechanisation and changes to the UK economy which led to a reduction in UK industry and possibly shift work before growing with the development of the service sector. To prevent double accounting of flight personnel who may be exposed to shift work patterns (see Section 3.3), flight personnel numbers from LFS 1979 data in Table 14 below (13,566) are subtracted from the shift work numbers to generate a conservative estimate of 387,045 female non-flight personnel night workers.

Table 11: Numbers of women in employment undertaking shift work, Great Britain, 2002‡

Type of shift pattern	Numbers employed	95% CI (+/- change)
All women usually/sometimes doing shift work	1,803,947	1589
Three-shift working ('slow' rotation through 3-shift system morning-afternoon-night)*	221,603	557
Continental shifts (rapid rotation through 3-shift system morning-afternoon-night)*	18,209	160
Two-shift system early/late-double day (2-shift system – day only)	562,849	888
Sometimes nights, sometimes day (2-shift system rotating between day and night)*	169,483	487
Split shifts (one shift split across day: night-work possible)	90,381	356
Morning shifts (day only)	47,543	258
Evening/twilight shifts (until midnight)	121,168	412
Night shifts (6 pm - 6 am, includes after midnight)*	154,400	465
Weekend shifts (6am – 6 pm only – day)	24,639	186
Other types of shift work (if different from above)	390,872	740

‡Source: IEH (2005) after ONS LFS (available at http://www.eoc.org.uk/cseng/research/statistics_on_shift_work.asp but website no longer live)
*Indicates definite night-work within the shift pattern

Table 12: Numbers of women in employment undertaking shift work according to LFS, UK, 1992-2007

Year	Total women employed (1000s)	% Shift work	No. women shift workers
1992	25,766	11.2	1,282,042
1993	25,478	11.8	1,351,973
1994	25,677	12.4	1,428,654
1995	25,989	12.6	1,462,747
1996	26,281	13.0	1,534,078
1997	26,744	13.6	1,630,191
1998	27,051	13.6	1,642,880
1999	26,732	14.1	1,727,236
2000	27,088	14.3	1,777,762
2001	27,334	16.1	2,024,591
2002	27,483	16.1	2,048,210
2003	27,744	16.7	2,138,318
2004	27,929	16.2	2,095,535
2005	28,187	15.8	2,068,252
2006	28,337	16.0	2,109,280
2007	28,441	16.5	2,179,716

(c) AF calculation:

The estimated total attributable fraction (female only) for cancer of the breast associated with shift work is 4.53% (95%CI= 3.23-5.94), which equates to 552 (95%CI= 393-724) attributable deaths and 1,957 (95%CI= 1,395-2,568) attributable registrations (Table 13).

Table 13 Summary results for shift work

				Data		Calculations				Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	AF	LL	UL	AN	LL	UL	AR	LL	UL
Women	Megdal *et al.* (2005)	H (i.e., night shift)	All		387045			1953645	0.0930	0.0453	0.0323	0.0594	552	393	724	1957	1395	2568
		H (i.e., night shift)		1.51	387045	0.9	0.14	1953645	0.0930	0.0453	0.0323	0.0594	552	393	724	1957	1395	2568
		All	All		387045			1953645	0.0930	0.0453	0.0323	0.0594	552	393	724	1957	1395	2568

1. Specific scenario or main industry code (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover(TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.3 FLIGHT PERSONNEL

(a) Risk estimate:

While not specifically included as a category by IARC, female flight personnel are considered an occupational group exposed to ionising radiation (cosmic source) and shift-work. It has been questioned whether flight personnel do shift work at all but the crossing of time zones during long-haul flights may be considered to have a disruptive influence on circadian rhythm; even short-haul flights in late evening will constitute shift work. While long-haul flights result in the highest individual exposures to ionising radiation, high numbers of short-haul flights over a long period of employment can also result in a high cumulative exposure. Due to the potential confounding from exposure to shift work and ionising radiation, flight personnel can be considered as a separate category.

A number of studies have reported risk estimates for flight personnel. The risk estimates vary for incidence and mortality and it has been suggested that exposures vary according to flight routes and length of employment. As such, European studies are more appropriate to the UK work force, with non-significant SMRs of 1.0 (95% CI 0.1-3.7) and 1.11 (95% CI 0.82-1.48) reported for two cohorts of flight personnel (Paridou *et al,* 2003; Zeeb *et al,* 2003), consistent with the findings of Ballard *et al,* (2002) and Blettner *et al,* (2002) which may be expected from the good survival rates seen for breast cancer. Incidence of breast cancer among female flight attendants in Europe has been shown to be higher. Rafnsson *et al,* (2001) considers a number of confounding effects associated with reproductive history for a significant SIR of 1.6 (95% CI 1.0-2.4) after a 15-year lag time; this increased to SIR = 4.1 (95% CI 1.7-8.5) for periods of employment in excess of 16 years. Pukkala *et al,* (1995) also reports a significant SIR of 1.87 (95% CI 1.15-2.23) which increases with increasing employment time. Haldorsen *et al,* (2001) and Linnerjo *et al,* (2003) record non-significant slight elevations in incidence risk, SIR = 1.1 (95% CI 0.8-1.5) and SIR = 1.3 (95% CI 0.85-1.74). Four meta-analyses report meta-RR for breast cancer incidence to be approximately 1.40 (Ballard *et al,* 2000; Megdal *et al,* 2005; Buja *et al,* 2006; Tokumura *et al,* 2006); Megdal *et al,* and Buja *et al.* both use the same studies to derive meta-RR but their results differ slightly due to different treatment of the individual risk estimates; the Megdal and coworkers (2005) meta-RR is arguably the more accurate as it uses the RRs as they are provided in each study for the meta-analysis rather than rounding to two significant figures (Buja *et al,*. 2006). As the metaSIR of 1.44 refers to any employment as flight personnel, the difference between long- and short-haul is no longer relevant.

(b) Numbers exposed:

The number of flight personnel employed in Great Britain for the years 1979, 1985, 2003 and 2004 according to the LFS are provided in Table 14. The description “air travel assistants” could include airport based personnel; the 1985 description “air transport” could include pilots, cabin crew, ground staff and others involved in air transport. As further division of the LFS descriptors is not available, the separation of ground staff from cabin crew/pilots, referred to here as flight personnel, cannot be accurately provided. Table 14 also provides data available from the Civil Aviation Authority (CAA) of the number of employees employed in particular roles within UK-based airline companies from 1997. While the employees may not all be UK residents, CAA figures are similar to LFS numbers.

For female air stewardesses, full data of numbers employed since 1958 was available from the British Airways Stewards and Stewardesses Union (BASSA, for women only). Noting that in 2003 the number of women stewardesses employed by BA (11,479) was 48% of the LFS 'air travel assistants' total (23,890), and 55% of the CAA 'cabin attendants' total (20,761) (Table 14), doubling the BA numbers of new starters during the REP gives an appropriate estimate of stewardesses ‘ever employed’ in the period (13,902 in 1956-95). These ‘ever exposed’ numbers for air stewardesses are given in Table 15, and are used in the estimation of AF for this part of the exposed population (bypassing the usual turnover equation estimate). However the estimate of 13,566 from LFS data

was more appropriately used to adjust the number of women shift workers to avoid double counting of women flight personnel (see shift work numbers exposed section above).

(c) AF calculation:

The estimated total attributable fraction (female only) for cancer of the breast associated with work as flight personnel is 0.03% (95%CI= 0.02-0.04), which equates to 4 (95%CI= 2-5) attributable deaths and 13 (95%CI= 7-19) attributable registrations (Table 15).

Table 14: Numbers of female flight personnel (cabin attendants and pilots/cockpit personnel) according to LFS and CAA, 1979 to 2005. Numbers for CAA refer to personnel employed by UK-based airline companies but need not be resident in the UK

	LFS				CAA		
Job description	**1979**	**1985**	**2003**	**2004**	**1997**	**2003**	**2005**
32.1 Aircraft flight deck officer	0						
67.3 Supervisors of travel stewards and attendants	329						
69.1 Travel stewards and attendants	13,237						
7500 Air transport		23,296					
3512 Aircraft pilots and flight engineers			137	0*			
6214 Air travel assistants			23,890	26,978			
Cabin attendants					18,765	20,761	23,189
Pilots, co-pilots, etc.					196	404	554
Total					18,961	21,165	23,743

*Figure too small to report

Table 15 Summary results for flight personnel

				Data		Calculations				Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
	Risk Estimate Reference	**Exposure**	**Main Industry Sector[1]**	**RR[2]**	**Ne[3]**	**Carex adj[4]**	**TO[5]**	**NeREP[6]**	**PrE[7]**	**AF**	**LL**	**UL**	**AN**	**LL**	**UL**	**AR**	**LL**	**UL**
Women	Megdal *et al.* (2005)	H	G-Q	1.44	n/a	n/a	n/a	13902	0.0007	0.0003	0.0002	0.0004	4	2	5	13	7	19
		H	All		n/a			13902	0.0007	0.0003	0.0002	0.0004	4	2	5	13	7	19
		All	All		Na/			13902	0.0007	0.0003	0.0002	0.0004	4	2	5	13	7	19

1. Specific scenario or main industry code (Table A1)

2. Relative risks selected from the "best study"

3. Numbers exposed, allocated to women. For the estimates of flight personnel based on BASSA cohort data, this estimate was not required as the cohort consisted of numbers ever exposed

4. CAREX adjustment factor to mid-REP REP (Table A1)

5. Staff turnover (TO, Table A1)

6. Number ever exposed during the REP (Statistical Appendix equation 3).

7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)

8. Statistical Appendix equation 1

4 OVERALL ATTRIBUTABLE FRACTION

4.1 EXPOSURE MAP

No overlap occurs between the substances and carcinogens relevant for breast cancer and so no exposure map is presented.

4.2 SUMMARY OF RESULTS

The results are summarised in Table 16 and Table 17

Table 16 Summary of RRs used to calculate AF

Agent	Exposure	RR	LL	UL
Flight personnel	H	1.44	1.26	1.65
Shift work	H	1.51	1.36	1.68

Table 17 Results

Agent	Numbers Ever Exposed	Proportion Ever Exposed	AF	MCLL	MCUL	Attributable Deaths	Attributable Registrations
Flight personnel	13902	0.0007	0.0003	0.0002	0.0004	4	13
Shift work	1953645	0.0930	0.0453	0.0323	0.0594	552	1957
Totals*			**0.0456**	**0.0326**	**0.0597**	**555**	**1969**

*Totals are the product sums and are not therefore equal to the sums of the separate estimates of attributable fraction, deaths and registrations for each agent. The difference is especially notable where the constituent AFs are large.

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6 STATISTICAL APPENDIX

Formulae used in the estimation of AF

Levin's equation

$$AF = Pr(E)*(RR-1)/\{1+Pr(E)*(RR-1)\} \quad (1)$$

where RR = relative risk, Pr(E) = proportion of the population exposed

A common denominator is used across exposure levels and industries for each exposure

Miettinen's equation

$$AF = Pr(E|D)*(RR-1)/RR \quad (2)$$

where Pr(E|D) = proportion of cases exposed (E = exposed, D = case)

Turnover equation to estimate numbers ever employed during the REP

$$N_{e(REP)} = \sum_{i=a}^{i=b} l_{(adj15)i} * n_0/(R-15)\} + \sum_{k=0}^{k=(age(u)-age(1))} \sum_{j=c+k}^{j=d+k} \{l_{(adj15)j} * n_0 * TO /(age(u)-age(l)+1)\} \quad (3)$$

where $N_{e(REP)}$ = numbers ever employed in the REP

n_0 = numbers employed in the exposed job/industry at a mid-point in the REP

TO = staff turnover per year

R = retirement age (65 for men, 60 for women)

$l_{(adj15)i}$ = the proportion of survivors to age i of those alive at age 15 (from GB life tables)

a to b = age range achieved by the original cohort members by the target year (2004) (e.g. 65 to 100 for the solid tumour REP)

c to d = age range achieved by the turnover recruited cohort members by the target year (25 to 64 for the solid tumour REP)

age(u) and age(l) = upper and lower recruitment age limits (24 and 15)

The derivation and assumptions underlying this formula are described in the methodology technical report, available on the HSE website. The equation can be represented as a single factor acting as a multiplier for n_0, calculated by setting n_0 to 1 in the above equation, so that the factor varies only with TO see Table A1 below.

Equation to estimate the proportion of the population exposed

$$Pr(E) = N_{e(REP)} / N_{p(REP)} \quad (4)$$

where $N_{p(REP)}$ = numbers ever of working age during the REP from population estimates for the relevant age cohorts in the target year

Equation for combining AFs where exposed populations overlap but are independent and risk estimates are assumed to be multiplicative:

$$AF_{overall} = 1- \Pi_k(1-AF_k) \text{ for the k exposures in the set} \quad (5)$$

Table A1 Employment level adjustment and turnover factors used in the calculation of AF

		Main Industry Sector	Adjustment factor for change in employment levels*	Turnover per year
Men	A-B	Agriculture, hunting and forestry; fishing	1	7%
	C-E	Mining and quarrying, electricity, gas and water; manufacturing industry	1.4	9%
	F	Construction	1	12%
	G-Q	Service industries	0.9	11%
		Total	1	10%
Women	A-B	Agriculture, hunting and forestry; fishing	0.75	10%
	C-E	Mining and quarrying, electricity, gas and water; manufacturing industry	1.5	14%
	F	Construction	0.67	15%
	G-Q	Service industries	0.8	15%
		Total	0.9	14%

* Applied to CAREX data for the solid tumour REP only. Exposed numbers are obtained for a mid-point year in the REP where national employment data sources have been used (the LFS or CoE).

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The burden of occupational cancer in Great Britain

Breast cancer

The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer was the attributable fraction (AF) being the proportion of cases that would not have occurred in the absence of exposure; and the AF was used to estimate the number of attributable deaths and registrations. The study involved obtaining data on the risk of the cancer due to the exposure of interest, taking into account confounding factors and overlapping exposures, as well as the proportion of the target population exposed over the relevant exposure period. Only carcinogenic agents, or exposure circumstances, classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens were considered. Here, we present estimates for cancer of the breast that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005. Due to the dominance of female breast cancer and the limited data concerning male breast cancer, this report focuses on breast cancer in women.

The estimated total attributable fraction (female only) for cancer of the breast attributable to occupation overall and associated with shift work (including flight personnel) is 4.56% (95%Confidence Interval (CI)=3.26-5.97), which equates to 555 (95%CI= 397-727) attributable deaths and 1,969 (95%CI=1,407-2,579) attributable registrations.

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