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Cancer and laterality: a study of the five major paired organs (UK)

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Abstract
Objective The human body displays marked asymmetry: paired organs differ bilaterally exerting effects upon cancer incidence and progression. However the factors involved remain contentious. In this large study involving over a quarter of a million cancer patients, we examine the epidemiological correlates of cancer laterality including incidence, stage at diagnosis and survival in the five major paired organs: the breasts, lungs, kidneys, testes and ovaries.
Methods Cancer patients were selected from the Thames Cancer Registry database and age-standardised incidence rates (ASRs), stage distribution at diagnosis and survival rates computed, stratifying appropriately.
Results Cancer incidence differed significantly by laterality at all sites studied ($p < 0.01$) but substantially in the lung (left–right incidence-rate ratio [IRR] 0.87), breast (IRR 1.07), testis (IRR 0.87) and in ovarian cancer (IRR 0.86). Autopsy data showed strongly coincident left–right organ size ratios (0.87 in the lungs and 0.87 in the testes). Patients with left testicular cancer, right lung cancer and left ovarian cancer showed significantly better survival than those with contralateral disease ($p < 0.05$).
Conclusions In the lungs and testes, asymmetries in cancer incidence closely coincided with asymmetries in organ size. Our results suggest that tissue mass in these organs is an important contributor to asymmetry in cancer incidence.

Keywords Laterality · Cancer · Incidence · Stage · Survival · Asymmetry

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Introduction

The internal anatomy of the human body displays marked asymmetry. Paired organs are not exempt from this asymmetry, and indeed often differ bilaterally in their tissue volume, structure, position, arterial supply, venous and lymphatic drainage, and in their anatomical and physiological relation to other organs. Behavioural factors such as handedness and more complex sociological phenomena may introduce further functional, diagnostic and treatment-specific asymmetry.

A relative excess incidence of left over right breast cancer is well documented, but controversy exists over whether this excess is, as is suggested by some authors, confined to women of greater than 45 years of age [1–3]. Similarly, studies reporting on asymmetries in cancer incidence at other sites including the lungs [4, 5], kidneys [6] and testes [7] provide evidence of asymmetry at the level of incidence at these sites. However, few studies have examined the effects of laterality on other epidemiological correlates such as the stage of cancer at diagnosis and survival.

In this large study of a UK cohort involving over a quarter of a million cancer patients, we examine the epidemiological correlates of cancer laterality in five major paired organs: the breasts, lungs, kidneys, testes and ovaries. The effects of laterality on the incidence, stage at diagnosis and survival of these cancers are explored.

Materials and methods

The Thames Cancer Registry is a population-based registry which collects data on cancer in residents of South East England including London (currently a population of 14 million). Data collection began in 1960 in the South

Thames Region and was extended in 1985 to also cover the North Thames Region. The patients registered at the TCR represent a cohort of individuals followed up from diagnosis to death, and the database currently contains over 1.5 million incident cancers.

The TCR database was used to identify all unilateral cancers of the lung, breast, kidney, ovary and testis that were diagnosed between 1985 and 2002 except in the case of ovarian cancers, where bilateral cases were included as a separate group. Of ovarian cancers, germ cell and non-germ cell tumours were considered separately. Only females with tumours of the breast were included in the analysis.

Age-standardised incidence rates (ASRs) were calculated for each combination of sex, laterality and cancer site. Cancer survival was computed by period analysis [8]. Differences in survival were tested for significance using the method described by Esteve et al. [9]. With breast and lung cancers, sex, laterality and site-specific subgroups were further subdivided into surgery and radiotherapy groups, depending on whether patients had received either of these treatment modalities as part of their management. Survival analysis was performed on these groups independently.

To compare stage at diagnosis, the percentage distribution of stage at diagnosis was calculated for each side independently.

Results

Of a total of 306,214 patients with cancers at any of the sites under investigation, 44,635 patients were excluded from the analysis because the laterality of the primary tumour was unknown or indicated as bilateral, leaving 261,579 patients with unilateral tumours of known laterality.

Table 1 shows the age-standardised incidence rates (ASRs) of cancers occurring at the sites of study. Figure 1 shows the corresponding age-specific rates. Figure 2 shows the distribution of cancer stage at diagnosis and Table 2 shows a survival analysis of cancers occurring at the sites of study by laterality.

At all sites of study, we found a statistically significant difference in cancer incidence between the left and right sides ($p < 0.01$).

Lung

A total of 67,018 males and 35,247 females with lung and bronchus cancers of known primary laterality were included in the analysis.

In males, the age-standardised incidence rate of cancer of the left lung was 24.5 (95% confidence interval [CI] 24.3–24.8) while that of the right lung was 27.8 (95% CI 27.5–28.1). In males, the mean mass at autopsy of the left lung was found by Grandmaison et al. [10] to be 583 g (95% CI 376–799) whilst that of the right lung was 663 g (95% CI 424–902). This yields a left to right incidence rate ratio (IRR) of 0.88 and a size ratio also of 0.88.

In females, the age-standardised incidence rate of cancer of the left lung was 10.0 (95% CI 9.8–10.1) while that of the right lung was 11.5 (95% CI 11.3–11.7). In females, the mean mass at autopsy of the left lung was found by Grandmaison et al. [10] to be 467 g (95% CI 293–641) whilst that of the right lung was 546 g (95% CI 339–753). This yields a left to right IRR of 0.86 and a size ratio also of 0.86.

Table 1 Age-standardised incidence rates of left and right cancers compared with published data on organ size. Sites where a statistically significant incidence rate ratio (at $p < 0.01$) was observed are emphasised in bold

Cancer site	Sex	ASR (95% C.I.)				Organ size (grams unless otherwise stated) (95% C.I.)				Incidence ratio (L/R)	Size ratio (L/R)	Source of organ size data
		Left		Right		Left		Right				
	Male	24.53	(24.25–24.80)	27.78	(27.49–28.7)	583	(376–799)	663	(424–902)	**0.88**	0.88	Ref. [10]
Lung	Female	9.95	(9.79–10.11)	11.54	(11.36–11.71)	467	(293–641)	546	(339–753)	**0.86**	0.86	Ref. [10]
Breast	Female	49.12	(48.73–49.50)	45.89	(45.57–46.26)	–		–		**1.07**	–	–
Breast (<50 years)	Female	12.60	(12.4–12.8)	11.90	(11.8–12.2)	–		–		**1.06**	–	–
Breast (≥50 years)	Female	36.40	(36.1–36.8)	33.90	(33.6–34.2)	–		–		**1.07**	–	–
Testis	Male	2.26	(2.17–2.34)	2.61	(2.52–2.70)	15.85 cm^3	(14.50–17.20)	17.50 cm^3	(15.90–19.10)	**0.87**	0.91	Ref. [11]
Ovary	Female	3.49	(3.39–3.59)	3.54	(3.44–3.64)	–		–		**0.99**	–	–
Ovarian GCC	Female	0.09	(0.07–0.11)	0.10	(0.09–0.12)	–		–		**0.86**	–	–
	Male	3.34	(3.23–3.44)	3.47	(3.37–3.58)	160	(119–201)	162	(123–201)	**0.96**	0.99	Ref. [10]
Kidney	Female	1.50	(1.44–1.57)	1.60	(1.53–1.66)	136	(99–173)	135	(96–174)	**0.94**	1.01	Ref. [10]

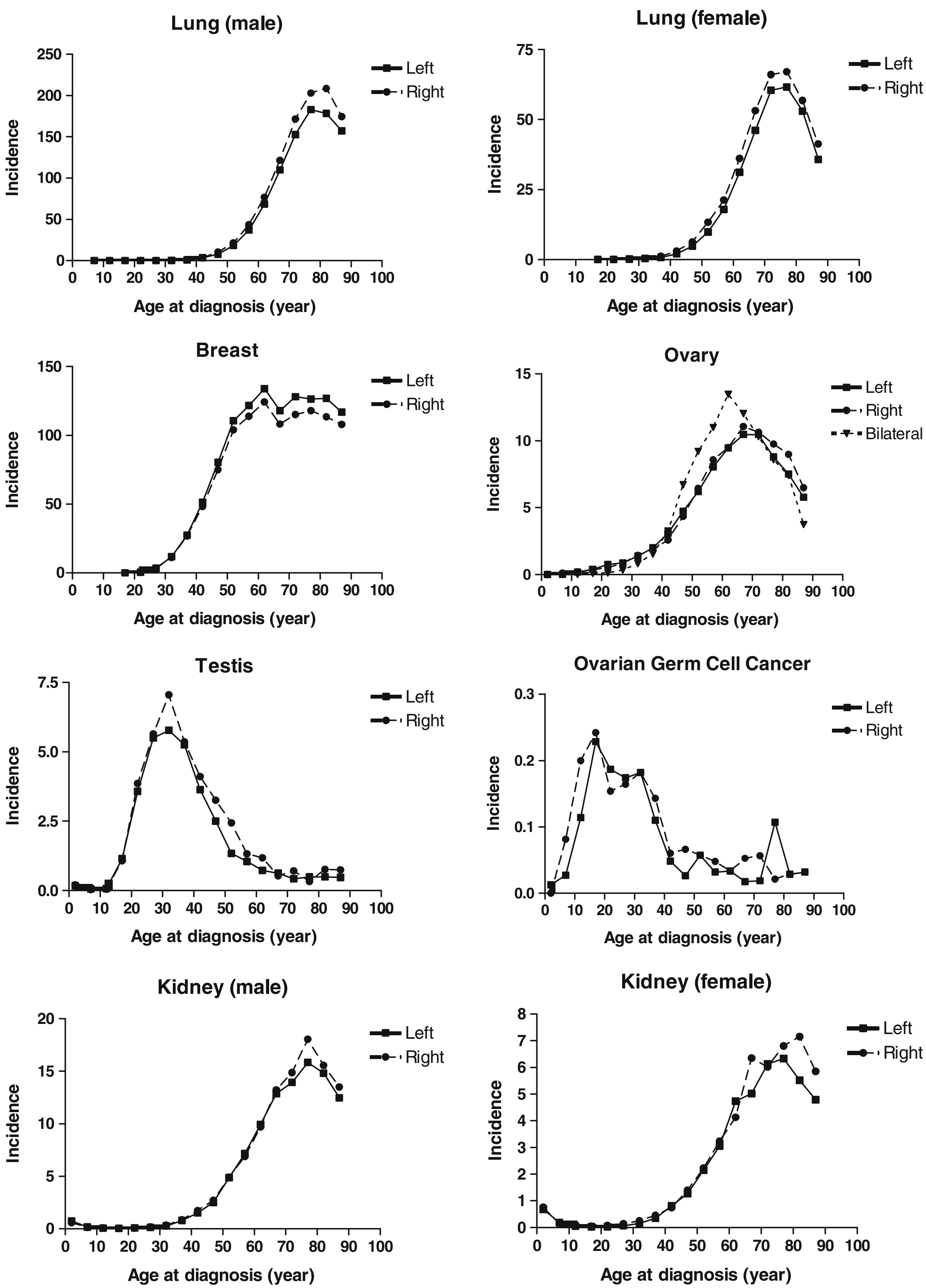

Fig. 1 Age-specific incidence rates of cancers occurring at the sites of study, by laterality. Bilateral cancers of the ovary are shown as a separate group

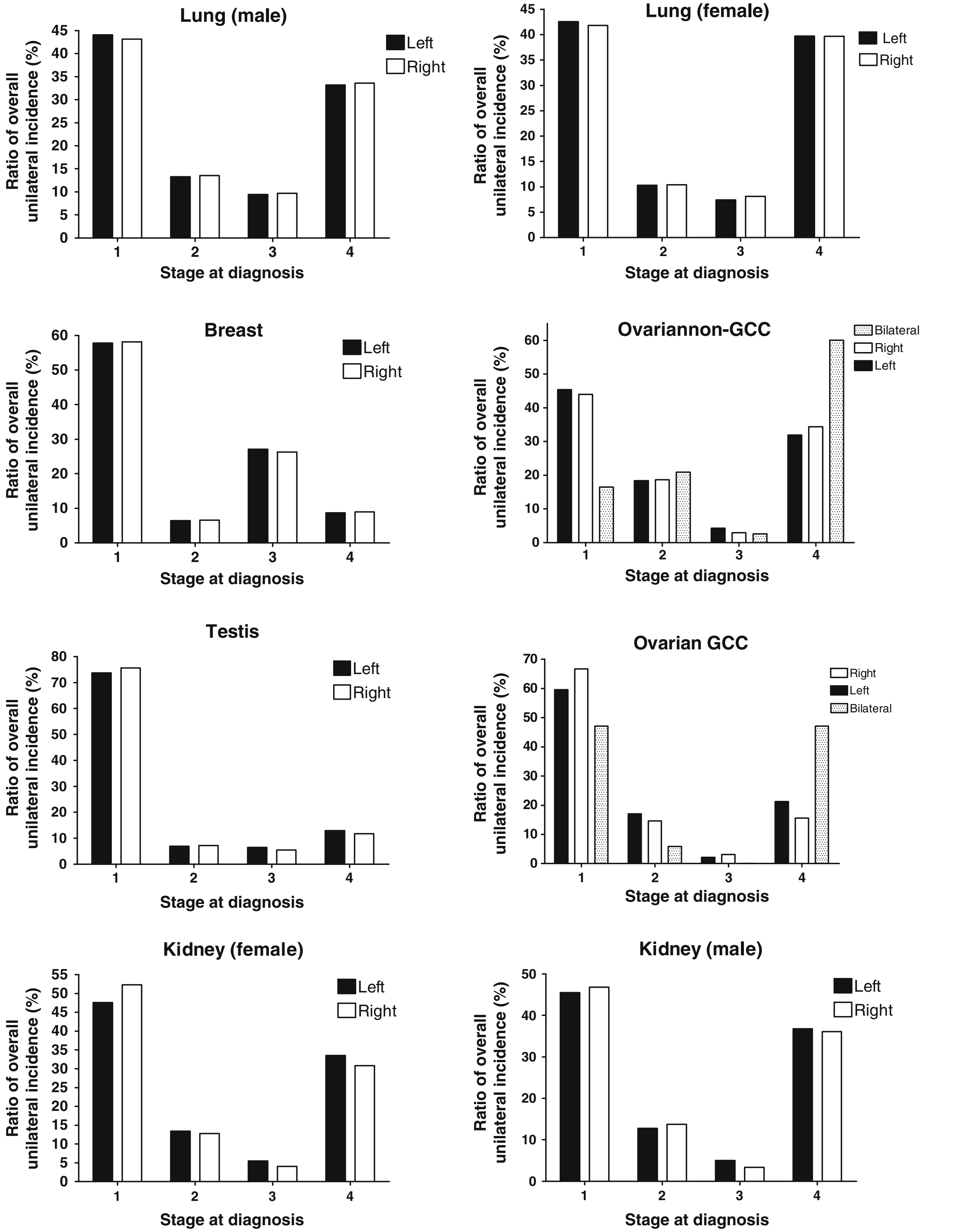

Fig. 2 Stage-distribution of cancers occurring at the sites of study, by laterality. The percentage contribution of each stage was calculated for each side independently. Stage 1: localised tumour; Stage 2: local spread of tumour; Stage 3: local lymph nodes involved; Stage 4: metastatic disease. Bilateral cancers of the ovary are shown as a separate group

The excess in right-sided lung cancers was consistent in all age groups.

Breast

A total of 130,370 women with breast cancer of known laterality were included in the analysis.

The age-standardised incidence rate of cancer of the left breast was 49.1 (95% CI 48.7–49.5) while that of the right breast was 45.9 (96% CI 45.6–46.3).

The excess in left breast cancer incidence was significant in both those over 50 and those under 50 years of age ($p < 0.05$), but the excess was slightly greater in those over 50 years (7.4% versus 5.8%).

Testis

A total 6,097 men with cancers of known laterality were included in the analysis.

The age-standardised incidence rate of testicular cancer of the left testis was found to be 2.3 (95% CI 2.2–2.3) while that of the right testis was 2.6 (95% CI 2.5–2.7). The mean volume of the left testis was found by Spyropoulos et al. [11] to be 15.85 cm^3 (95% CI 14.50–17.20) whilst that of the right testis was 17.50 cm^3 (95% CI 15.90–19.10). This yields a left to right IRR of 0.87 and size ratio of 0.91.

Ovary

Out of a total of 22,000 women with ovarian cancer, 21,712 women had non-germ cell tumours.

Amongst non-germ cell tumours, 9,512 were of known laterality, 5,198 were indicated as bilateral and 7,002 were recorded as of unknown laterality.

Amongst the 288 germ cell cancers (GCC), 242 were of known laterality while 20 were indicated as bilateral and 26 were indicated as of unknown laterality.

The age-standardised incidence rate of left and right-sided non-germ cell ovarian cancers were similar: 3.5 (95% CI 3.4–3.6) and 3.5 (95% CI 3.4–3.6) respectively yielding a left–right IRR of 0.99. The age-standardised incidence rate of left-sided ovarian germ-cell cancer was 0.09 (95% CI 0.07–0.11) while that for right-sided GCC was 0.10 (95% CI 0.09–0.12) yielding a left:right IRR of 0.86.

The excess of right-sided ovarian germ-cell cancers was evident in most age-groups.

Kidney

A total of 8,277 males and 4,699 females with kidney cancers of known primary laterality were included in the analysis.

In males, the age-standardised incidence rate of cancer of the left kidney was 3.3 (95% CI 3.2–3.4) while that of the right kidney was 3.5 (95% CI 3.4–3.6). The mass at autopsy of the left kidney was found by Grandmaison et al. [10] to be 160 g (95% CI 119–201) whilst that of the right kidney was 162 g (95% CI 123–201). This yields a left to right IRR of 0.96 and a size ratio of 0.99.

In females, the age-standardised incidence rate of cancer of the left kidney was 1.5 (95% CI 1.4–1.6) while that of the right kidney was 1.6 (95% CI 1.5–1.7). The mass at autopsy of the left kidney was found by Grandmaison et al. [10] to be 136 g (95% CI 99–173) whilst that of the right kidney was 135 g (95% CI 96–174). This yields a left to right IRR of 0.98 and a size ratio of 1.01.

The small excess of right-sided kidney cancer was only evident in the oldest age-groups.

Table 2 Five-year survival (as percentages) of cancers occurring at the sites of study, given by laterality. Sites where a statistically significant survival difference was observed ($p < 0.05$) are emphasised in bold

Organ	Five-year survival (95% CI) as percentages			
	Male		Female	
	Left	Right	Left	Right
Lung	4.01 (3.06–4.97)	4.24 (3.64–4.84)	**3.78 (2.76–4.81)**	**4.55 (3.77–5.32)**
Lung (RT+)	6.14 (5.38–6.90)	6.08 (5.40–6.76)	5.50 (4.55–6.44)	5.26 (4.44–6.07)
Lung (S+)	13.65 (12.50–14.81)	13.03 (11.96–14.1)	**16.30 (14.72–17.87)**	**14.57 (13.20–15.94)**
Breast	– –	62.42 (60.48–64.35)	61.89 (60.31–63.47)	
Breast (RT+)	– –	80.86 (79.95–81.78)	81.25 (80.32–82.19)	
Breast (S+)	– –	87.48 (86.72–88.23)	87.47 (86.69–88.25)	
Ovary (non-GCC)	– –	**52.32 (50.26–54.38)**	**49.51 (47.86–51.15)**	
Ovary (GCC)	– –	89.89 (80.14–99.63)	88.95 (81.53–96.37)	
Testis	**98.20 (97.17–99.22)**	**96.94 (95.81–98.08)**	– –	
Kidney	48.26 (45.54–50.97)	48.55 (45.82–51.28)	46.36 (42.93–49.79)	43.33 (39.97–46.69)

Breast and lung cancer groups are further subdivided into those where radiotherapy was delivered as part of treatment (RT+) and those where surgery was performed (S+)

Stage distribution and survival

Figure 2 shows the percentage stage distribution at diagnosis of left- and right-sided cancers.

Table 2 shows 5-year survival rates of patients with either left- or right-sided cancers occurring at the sites of investigation. Those who received surgery as part of their treatment (S+) and those who received radiotherapy as part of their treatment (RT+) are considered separately. In women, 5-year survival was significantly higher in patients with left when compared with right-sided lung cancer ($p < 0.01$), a difference that persisted in surgically treated patients (16.3% versus 14.6%; $p < 0.05$). Five-year survival was also significantly higher for left-sided ovarian cancers compared to right-sided cancers, but the difference was not substantial (52.3% versus 49.5%; $p < 0.05$). In males, 5-year survival was significantly higher in left sided testicular cancer (98.2% versus 96.9%; $p < 0.01$).

Discussion

In this study, we have investigated the effect of primary laterality on the incidence, stage at diagnosis and subsequent survival of cancers occurring in the five major paired organs of the body. It is important to note that while laterality data is considered accurate when reported, such data was not present in a proportion of cancer registrations, resulting in their exclusion from the analysis: out of 306,214 observed cancers at all sites under investigation, laterality could not be ascertained in 44,635 cases (15%). Reasons for the absence of laterality data include simple non-reporting of laterality or situations where primary laterality could not be ascertained due to advanced disease or multiple primary cancer. The latter situation is relatively rare except in the ovary in which 24% of cancers were recorded as bilateral. This is due to the relatively common late presentation of this cancer after which metastatic spread to the contralateral ovary is likely to have occurred, obscuring the original primary laterality. A large proportion of ovarian cancers were recorded as of unknown laterality. This is once again due to the late presentation of this disease, where palliation is often considered as the appropriate management, rendering investigation into primary laterality superfluous. In other cancers, it is rarer that the presence of metastases in the contralateral organ should obscure the true primary laterality of the cancer: Only 1% of cancers other than those of the ovary were reported as being primarily bilateral.

In this study, we have used period analysis to obtain survival estimates. Period analysis, of actuarial origin, is a life table method of calculating survival that allows the inclusion of recent follow-up data.

In the case of lung cancer, the left–right incidence rate ratio coincided strikingly with the left–right size ratio both in males and females with the larger right lung displaying a proportionately higher cancer incidence. Lung mass at autopsy was thought to be the most appropriate data to use to establish tissue mass in the case of the lungs. Lung volume in living subjects was considered unsuitable since a non-linear tissue-mass to organ-volume relationship, and pressure differentials across an asymmetrical mediastinum on either side might result in a poor representation of tissue amount by lung volume. However, another consideration in the case of lung cancer is differential left–right exposure to inhaled cigarette smoke resulting from a difference in tidal volume. This might be expected to correlate with lung size, and it could be speculated that this relationship would approximate linearity.

In females, a left–right incidence ratio was also observed in the breast, with the incidence of left breast cancer being higher. We could not locate reliable data comparing breast size by laterality, possibly since breast volume fluctuates with the ovulatory cycle rendering difficult the representative estimation of mean volume. Certainly however, some authors have speculated that the left breast is larger than the right breast [12]. These authors also reported a positive relationship between inter-individual breast size and breast cancer incidence but found that this relationship was found only amongst post-menopausal women. Egan et al. [13] have found a similar increase in post-menopausal breast cancer incidence, but one which is limited to women with a lean body mass perhaps in whom breast size is a truer reflection of the at-risk gland-mass and is not obscured by additional fatty tissue. It has not been established whether the difference in left–right breast cancer incidence similarly results from a difference in the mass of glandular breast tissue but this remains likely. In our study, the left-sided excess was significant in those both over 50 and under 50 years of age, although we found that the left-sided excess in incidence was slightly more pronounced in women over 50 compared with those under 50 years of age (7.4% versus 5.8%). This age distribution of the observed excess resembles the earlier findings in inter-individual incidence [12].

Handedness is a factor that may exert behavioural and diagnostic asymmetries on breast cancer incidence. At a behavioural level, the breast ipsilateral to the dominant hand may be exposed to a greater degree of movement and therefore physical stress than the contralateral breast. Furthermore, handedness in nursing mothers may affect which breast is more frequently presented to infants for suckling. Indeed, a large study by the Collaborative Group on Hormonal Factors in Breast Cancer [14] have shown a modest protective role of lactation on breast cancer risk that was independent of parity, age at first delivery, menopausal status and other major risk factors for breast cancer. At a diagnostic level, handedness might asymmetrically affect womens' ability to detect early tumours either by inadvertent discovery or on self-screening thus delaying presentation and producing a tendency for breast cancers to present at an earlier stage on one side. However, we found no noteworthy differences in the stage at diagnosis of cancers of the left and right breast. Recent studies have suggested that left-handedness contributes to a constitutional, not an environmental, excess in breast cancer risk that is cancer laterality independent [15]. These authors have suggested hormonal exposure in utero to be contributory to this constitutional effect. In our study, we were not able to collect data concerning handedness.

Testicular cancer was found to be commoner in the right testicle when compared with the left, and a similar mass ratio has been reported, with the right testicle being larger [11]. Scrotal asymmetry also exists however, and the right testicle, in addition to being larger, is often higher, and thus being closer to the body, is subject to slightly higher temperatures [16]. It is not known whether this is a contributory factor in the higher right-sided incidence.

Cryptorchidism is an established risk factor for testicular cancer, but the right-sided excess in testicular cancer, established firmly in this study and elsewhere [7] does not seem to exist in cases of unilateral cryptorchidism. One large study found that at three months of age, 50.5% were in the left side and 49.5% were in the right side [17].

There are many similarities between male germ cell cancers in the testis and female germ cell cancers in the ovaries [18]. It is interesting to note that the right-side dominance in these cases is similar in males and females. Since epithelial ovarian cancers show no differential incidence by laterality, it is plausible that the excess incidence in the right gonad of germ cell cancers may have arisen by differential migration or clonal expansion of the primordial germ cell population from which male and female germ cell cancers arise.

The kidneys have been shown to be very similar in size bilaterally [10] and there was only a very slight difference in cancer incidence. Similarly, we found very little difference in incidence between left and right ovarian cancer.

When looking at cancers of the kidney, especially in females, there were slight differences in the stage-at-diagnosis profiles between the left and right sides, with a smaller proportion of left-sided tumours presenting early when compared with those of the right side. The most plausible explanation might be that cancer of the right kidney produces symptoms slightly earlier than cancer of the left kidney resulting in earlier presentation and diagnosis. Anatomical differences contributory to this might include that the right kidney is most commonly found to be lower in the abdomen when compared with the left kidney [19]. In our cohort, 5-year survival from renal cell cancers in females was found to be slightly, although not statistically significantly, reduced on the right side. In other organs, differences in the stage-at-diagnosis profile bilaterally were negligible.

Five-year survival from left-sided ovarian cancer was significantly greater than for right-sided disease, but the difference was not substantial (52.3% and 49.5% respectively). Right-sided testicular cancer patients showed a significantly lower survival than left-sided patients (96.9% versus 98.2%).

In women, survival from lung cancer was found to be significantly decreased in cancers of the left lung compared with those of the right, a difference that could be due to asymmetries in organ size and lymphatic drainage in the mediastinum. In addition, the difference was present in patients who underwent surgery as part of their treatment, but not in those who underwent radiotherapy. A significant asymmetry in lung cancer survival was not observed in males. Data on metastasis would be particularly useful in evaluating whether asymmetry in lymphatic drainage might contribute to the observed differences in survival between the left and right sides. However, we could not collect such data in our patient group, so this remains a potential subject for future study.

In this study we have examined the epidemiological correlates of cancer laterality in the five major paired organs of the body. We have found differences in cancer incidence by laterality to closely coincide with differences in organ size, very markedly in the lungs, both in males and females, and also in the testes and kidneys suggesting that organ size is an important factor underlying asymmetry in cancer incidence in these organs.

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